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THE SERUM TRANSAMINASE TEST IN VARIOUS DISEASES. ITS DIAGNOSTIC VALUE IN LIVER DISEASE

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THE usefulness of the serum glutamic-oxalacetic transaminase (SGO-T) test as devised by LaDue and his associates[1] appears to be well established in the diagnosis of myocardial infarction.[2-5] Intelligent interpretation of the test in any particular case, however, depends upon knowledge of its behavior in a wide variety of clinical disease states. It is essential to know whether the test may give abnormal results in conditions other than myocardial infarction.

The present communication lists the results of the SGO-T test in a variety of clinical situations. The data show that elevations of SGO-T may occur in a number of different diseases, particularly in liver disease in which the test appears to have diagnostic value.

MATERIAL AND METHODS

The material includes 111 patients studied on the wards of the Wadsworth Veterans Administration Hospital and the UCLA Medical Center. Serum transaminase activity was determined by the method of Karmen.[6] The upper limit of normal for SGO-T activity is 40 units as noted by LaDue[1] and in our earlier series.[7] Slight elevations of SGO-T between 40 and 50 units must be regarded as being of doubtful significance unless the time course of serial determinations is known.

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RESULTS

Patients With Pericarditis.—Eight cases of pericarditis were studied (Table I). Five of these were diagnosed as benign idiopathic pericarditis. They all had typical histories, pericardial friction rubs, and characteristic electrocardiographic abnormalities. All became well without specific treatment. Peak SGO-T levels in these 5 cases were normal, ranging from 20 to 29 units. Three pericarditis patients had SGO-T elevations. One was a 12-year-old child with acute rheumatic carditis and pericarditis with a peak level of 43. A 35-year-old man with recurrent rheumatic pericarditis reached a peak of 83 units. A 29-year-old man entered in a critically ill state with high fever, chest pain, a loud pericardial rub, and an electrocardiogram showing very marked elevations of ST segments in most leads. SGO-T reached a maximal level of 136 and gradually subsided as the patient recovered without specific therapy. He was believed to have had an unusually severe form of benign idiopathic pericarditis.

TABLE I. SGO-T LEVELS IN VARIOUS HEART AND LUNG DISEASES

NO ELEVATIONS		ELEVATIONS		
NO. OF CASES	DISEASE STATE	NO. OF CASES	DISEASE STATE	PEAK LEVEL
5	Idiopathic pericarditis	1	Acute rheumatic carditis and pericarditis	43*
2	Aortic stenosis	1	Recurrent rheumatic pericarditis	83
5	Congestive heart failure (2 in pulmonary edema)	1	Idiopathic pericarditis	136
1	Healed myocarditis			
1	Coarctation of aorta	1	Congestive failure, pulmonary infarct, very large liver	98
1	Mitral stenosis with atrial flutter	1	Congestive failure, pulmonary infarct	44*
1	Subacute bacterial endocarditis			
1	Acute rheumatic fever, no carditis	2	Terminal cyanosis and collapse due to valvular heart disease	237 292
1	Cardiac neurosis	3	Pulmonary infarct	54 53
2	Pulmonary infarct			52

*Doubtful significance.

Patients With Various Heart Diseases.—These cases are listed in Table I. Congestive heart failure in itself does not cause elevation of SGO-T, but congestive failure combined with a very large liver and pulmonary infarcts may cause elevation. It is not clear whether the infarcts or the liver involvement plays the predominant role.

In 2 cases of severe failure due to valvular heart disease, blood samples were taken only a few moments before death after several hours of cyanosis, stupor,

and a shocklike state. Both of these samples showed marked elevation of SGO-T. In view of LaDue's observation[2] that there is a rapid rise of SGO-T after death, it may be surmised that in these two terminal patients a certain amount of tissue dissolution had already taken place.

Patients With Pulmonary Infarction.—Five cases of pulmonary infarction were studied (Table I). Two of these which were associated with heart disease had elevations of SGO-T to 53 and 54 units. In the other 3 which were associated with thrombophlebitis the levels were 52, 36, and 28 units. Thus pulmonary infarction may cause a low-level rise of SGO-T which is not necessarily associated with heart failure or enlargement of the liver.

Patients With Pancreatitis.—Because pancreatitis may enter into the differential diagnosis of myocardial infarction, 4 patients with this disease were studied. None of them had jaundice or abnormal liver function tests. On admission, one patient with acute hemorrhagic pancreatitis had SGO-T level of 432 units which fell rapidly to 28 units by the fifth hospital day. Another patient with recurrent pancreatitis had levels of 80, 102, and 80 on successive days. A patient who had acute pancreatitis associated with subacute bacterial endocarditis proved at autopsy had a peak level of 70. One other patient with chronic pancreatitis had a normal level of 30 units. Thus, acute pancreatitis may produce a curve of SGO-T elevation similar to that seen in acute myocardial infarction. The test would therefore not be of value in the differential diagnosis between these two diseases. We have not observed extremely high levels of SGO-T in pancreatitis as described by Denney and co-workers.[8]

Patients With Liver Disease.—This group consists of 30 patients divided into four subgroups as shown in Fig. 1; hepatitis, 9 cases of which 2 were the homologous serum type; obstructive jaundice 6 cases; Laennec's cirrhosis with jaundice 10 cases (one with hemochromatosis), and without jaundice 5 cases.

Peak values of SGO-T in the individual cases of the four groups are plotted in Fig. 1. Hepatitis produced the highest levels seen in the series. There was no difference in the behavior of the SGO-T levels between the naturally acquired type of disease and the homologous serum type. Of the two highest values obtained, 1890 and 1530, one of each type was represented. The 2 patients indicated by open circles were tested only in the late convalescent period.

Fig. 2 illustrates the curve of values for SGO-T obtained in a patient who developed homologous serum hepatitis following mitral commissurotomy. The peak level of SGO-T occurred on the seventeenth day after the clinical onset of the disease, and elevations of SGO-T persisted until the fifty-third day of disease. It is unlikely that such a curve could be confused with one due to myocardial infarction in which elevations of SGO-T seldom persist for more than 6 days. It is of interest that the rise and fall of SGO-T in no way paralleled the levels of the serum bilirubin, for SGO-T continued to rise for 9 days while the bilirubin was falling. This patient at no time had elevation of thymol turbidity or a positive cephalin flocculation test.

It is interesting to compare the two patients who had peak levels of 458 and 474. Although both had similar SGO-T levels, one was deeply jaundiced while the other had no jaundice even though his thymol turbidity was 16 and his cephalin flocculation ranged from 3+ to 5+ (scale of 0 to 6+).

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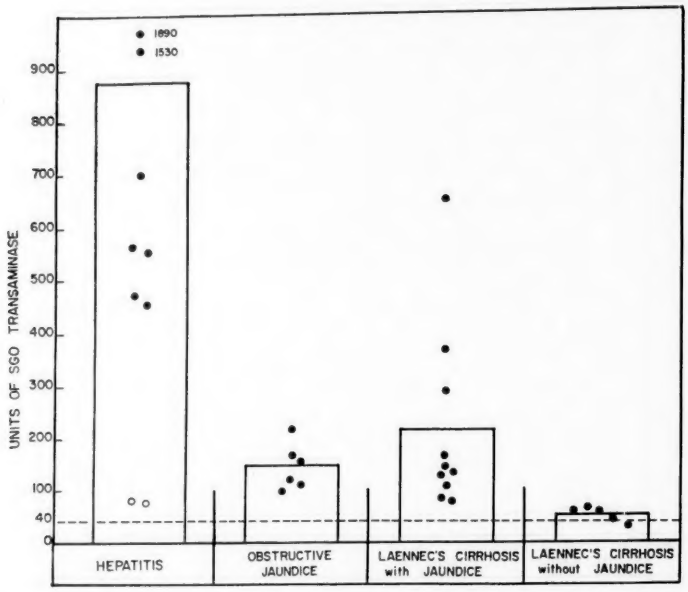

Fig. 1.—Peak SGO-T levels found in individual cases of various forms of liver disease. Height of column represents mean for the group. Open circles are two cases studied late in convalescent stage of disease.

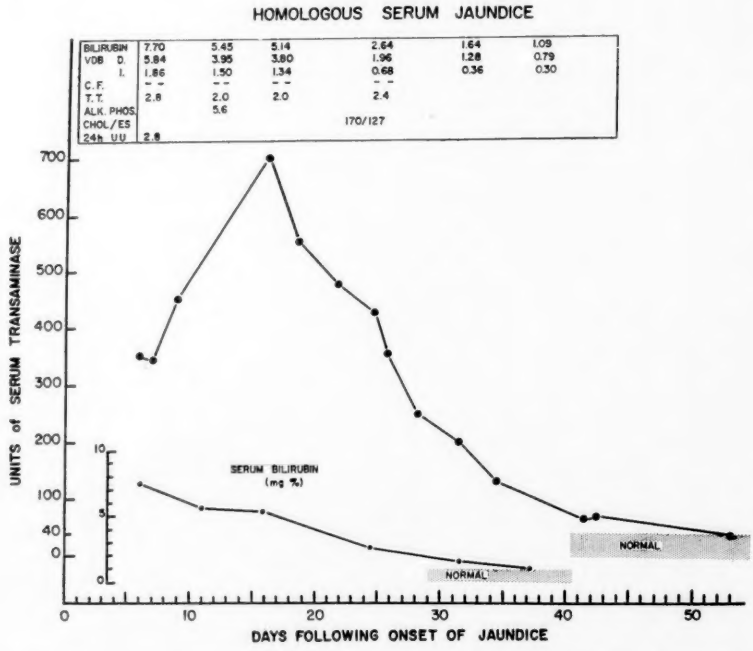

Fig. 2.—Plot of SGO-T levels and serum bilirubin in a case of homologous serum hepatitis. In box at the top values are given for serum bilirubin, Van den Bergh direct and indirect, cephalin flocculation, thymol turbidity, alkaline phosphatase, cholesterol and cholesterol esters, and 24-hour urine urobilinogen.

Among 6 patients with obstructive jaundice there were 2 with stricture of the common bile duct, 1 with stone in the common duct, 1 with cholangiolitis, 1 with carcinoma of the head of the pancreas, and 1 with chlorpromazine jaundice. All patients had elevations of SGO-T but the highest peak value was 210 and the lowest peak was 104. The peak values in this group never approached the height of the levels found in hepatitis. Fig. 3 illustrates the variations in the SGO-T during the last few days of life of a patient who was admitted to the hospital in a comatose state with deep jaundice and bronchopneumonia. The low-level flat curve is highly suggestive of obstructive jaundice rather than hepatitis, and at autopsy an impacted stone was found in the common bile duct. Unfortunately it was not possible to obtain postoperative studies on the patients who had surgical correction of their biliary obstruction.

Fifteen patients with cirrhosis of the liver were studied. One of these was later shown to have hemochromatosis. In 5 cases there was no jaundice at the time of the study. These 5 had peak SGO-T levels of 34, 40, 46, 48, and 60, representing normal to slightly elevated levels. One of these patients had ascites due to portal hypertension.

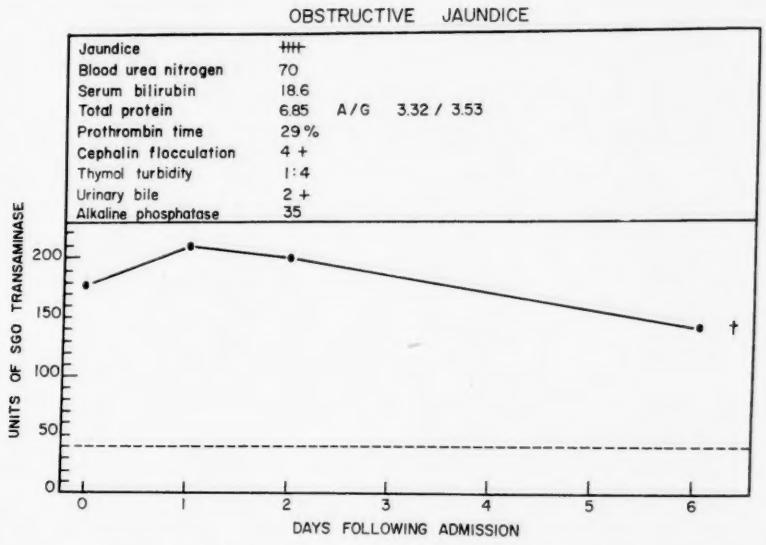

Fig. 3.—SGO-T levels and liver function tests in a case of obstructive jaundice due to stone in the common duct.

Among the jaundiced patients with cirrhosis there were 7 who had peak levels of SGO-T varying from 83 to 156 units. The patient with hemochromatosis is included in this group. These all had low-level curves which bore no relationship to the degree of jaundice. They appeared to behave much like the patients with obstructive jaundice. One of these cases is illustrated in Fig. 4. The other 3 patients of this group had peak levels of SGO-T much higher than those seen in obstructive jaundice and overlapping to some extent the levels found in hepatitis. In contrast to the other 7 cases in this clinical category these

latter 3 patients showed sharp declines in their high levels after the institution of therapy. For example the patient with a level of 654 was in hepatic coma. On treatment he recovered from his coma and his SGO-T level fell in the space of one week to 268. The patient with a level of 359 improved clinically as his SGO-T level fell over a 3-week period to 142. The other patient had a level of 294 on admission and by the next day it had dropped to 139 units. The latter 2 patients, however, died shortly therafter of massive hemorrhage from esophageal varices.

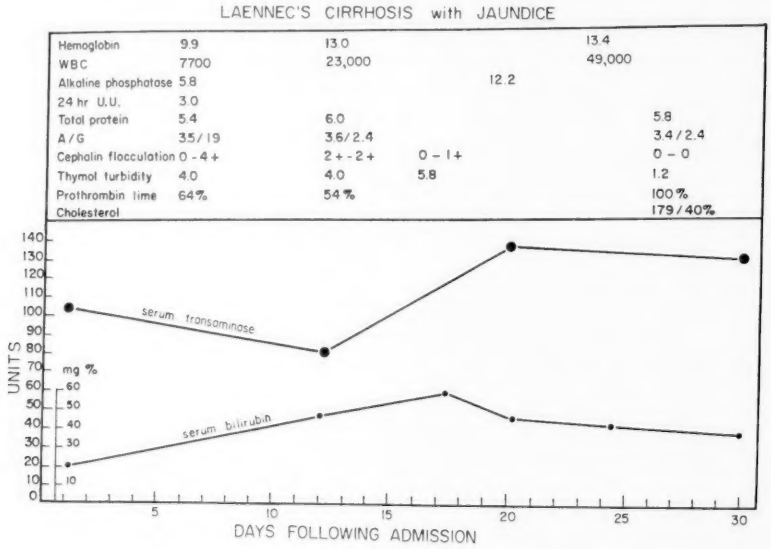

Fig. 4.—Plot of SGO-T levels and serum bilirubin in a case of cirrhosis of the liver with jaundice. Other laboratory data in box at top of chart.

The data from the cases of cirrhosis of the liver appear to indicate that the SGO-T levels may give some clue to the degree of activity of the underlying disease process. It is suggested that when the biliary obstructive process is dominant there is a rise of SGO-T to the level of 100 to 200 units, but when the cellular destructive process is dominant the levels may rise to higher values, perhaps in the 300 to 700 range comparable to levels found in hepatitis. In the quiescent stage of the disease when there is no biliary obstruction the levels may be at or near normal values even though evidence of portal vein hypertension as manifested by ascites may be present.

Patients With Malignant Disease.—This group is composed of 8 patients. Four of these, one each with lymphosarcoma, Hodgkin's disease, leiomyosarcoma, and carcinoma of the stomach with liver metastases without jaundice, had normal SGO-T levels ranging from 16 to 26. One patient with chronic lymphatic leukemia had a level of 47 units. The other three patients all had jaundice and extensive liver metastases with elevations of SGO-T. In one case of carcinoma of the stomach with metastases to the liver the levels of 86 and 84 units were obtained 3 days apart. In one case with widespread metastatic disease the primary tumor was not discovered at operation and no autopsy was performed. SGO-T's were

84, 104, and 109 units during the week before death. The last patient in the group had carcinoma of the bladder with metastases to liver, kidneys, and lungs. The peak level of SGO-T was 1,290 units just prior to death.

Patients With Miscellaneous Diseases.—These are listed in Table II. One patient with a cerebral vascular accident showed a definite though low-level elevation of SGO-T to 50 units which fell in the space of 2 days to 32 units. All three of the cerebral vascular accidents were diagnosed on clinical grounds as arterial thromboses.

TABLE II. SGO-T LEVELS IN MISCELLANEOUS DISEASES

ELEVATIONS			NO ELEVATIONS	
NO. OF CASES	DISEASE	PEAK SGO-T LEVEL	NO. OF CASES	DISEASE
1	Cerebral vascular accident	50	2	Cerebral vascular accidents
1	Muscular dystrophy	93	1	Pneumonia and emphysema
1	Acute gastritis and shock	60	1	Dissecting aneurysm
1	Infarcts of kidneys and brain	97	1	Chronic nephritis
1	Paroxysmal myoglobinuria	477	1	Diabetes mellitus
			1	Subphrenic abscess
	Slight Elevations of Doubtful Significance		1	Dermatomyositis
1	Scleroderma	42	1	Rib fracture
1	Diverticulitis of colon	44	1	Congenital hemolytic jaundice
1	Probable renal infarct	46		

Two patients with renal infarction were studied. One had only a slight SGO-T elevation of doubtful significance, while the other with a level of 97 units was complicated by cerebral infarction.

The patient who had an elevation of SGO-T to 60 units associated with a protracted period of shock had subsequent levels of 56, 40, and 30 over the next 3 days. The elevation in this case was attributed to the total body anoxia associated with shock. The cases of pneumonia, nephritis, and subphrenic abscess suggest that inflammation does not produce a rise in SGO-T.

A 19-year-old patient with congenital hemolytic jaundice admitted for splenectomy had a normal serum transaminase value of 28 units. He had mild scleral icterus, serum bilirubin of 5.4 and 3.8 mg. per cent, hemoglobin of 13.8 Gm. per cent, BSP test showed no retention, and cephalin flocculation was negative. The hemolysis of red cells in blood samples results in an elevation of the SGO-T and, therefore, higher levels might be expected in congenital hemolytic jaundice. This patient had an icteric serum, and yet the SGO-T was normal. Since cases of pulmonary infarction and dissecting aneurysm, both of which are also characterized by destruction of large numbers of red blood cells, have shown normal

levels or slight elevations of SGO-T, it is suggested that hemolytic processes are not capable of producing marked elevation of SGO-T.

Since skeletal muscle contains a large amount of transaminase it is not surprising that diseases which cause breakdown of this tissue would show elevation of SGO-T. The patient with muscular dystrophy showed a significant elevation but the case of dermatomyositis had a normal level, while the patient with scleroderma had only a slight elevation of doubtful significance.

A 46-year-old man with paroxysmal myoglobinuria was of great interest. This man experienced intensely painful muscle spasm in any group of muscles which were subjected to slightly more than routine stress. This would be followed within an hour by passage of red urine containing large amounts of myoglobin. Following a 10-second knee-bend and squat the patient developed bilateral spasm of the quadriceps muscle groups. An hour later the urine became red, and by the end of 24 hours he had become anuric. He remained so for 9 days and then recovered with profuse diuresis. SGO-T was followed for the first 24 hours. Before exercise the level was 33, ten minutes after exercise it was 30, thirty minutes after exercise, 43; two hours after, 56; 5 hours after, 203; 8 hours after, 477; 24 hours after, 410. Assays of serial urine samples for SGO-T activity revealed only negligible amounts varying from 4 to 10 units. Thus these peculiarly diseased skeletal muscles liberated large quantities of transaminase along with the myoglobin.

Effect of Surgical Procedures.—Because of the inevitable trauma to muscle and other tissues resulting from surgical operations, a group of 17 patients had serial determinations of SGO-T during the postoperative period. These are listed in Table III. Slightly more than half the patients who were followed showed elevations during the postoperative period with the peaks appearing one to 4 days after the operations.

Newborn Infants.—Cord blood was taken from 5 newborn infants. The levels of SGO-T in these blood samples were 26, 26, 27, 30, and 44. Slight hemolysis may have accounted for the one that was 44.

DISCUSSION

The data herein presented are indicative of the highly nonspecific nature of the SGO-T test. The great variety of disease states which may produce elevation of SGO-T makes it imperative that the clinician who attempts to apply the test to any individual case be reasonably able to exclude other causes for elevation.

Our observations are in general agreement with the findings of others.

Although Nydick and his associates[9] have found elevation of SGO-T in rheumatic pericarditis and carditis as we have, others have not found elevations in the benign idiopathic type of pericarditis. Our one severe case showed a significant elevation along with marked electrocardiographic changes. The findings suggest that if the pericarditis is severe enough to involve a significant amount of underlying heart muscle, elevation of SGO-T may result. Agress, Glassner, and Binder[10] have offered experimental proof for this view.

Cases similar to our two preterminal patients with marked SGO-T elevations were seen by Merrill and associates.[11]

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TABLE III. EFFECT OF SURGERY ON SGO-T

ELEVATIONS				NO ELEVATIONS	
NO. OF CASES	TYPE OF CASE	PEAK LEVEL	POST OP. DAY OF PEAK	NO. OF CASES	TYPE OF CASE
1	Colectomy	54	4	1	Subtotal gastric resection
1	Cholecystectomy	70	4	2	Varicose vein ligation and stripping
1	Appendiceal abscess drainage	150	4	3	Herniorraphy
1	Varicose vein stripping	57	4	1	Femoral artery aneurysm repair
2	Herniorraphy	43* 46*	4 2	1	Fibroma of left arm removal
3	Subtotal gastric resection	119 74 43*	3 2 1		

*Doubtful significance.

Although Agress, Glassner, and Jacobs[12] were not able to demonstrate a rise of SGO-T following experimental pulmonary infarction, we have seen several such patients with low-grade elevations. This finding makes the use of the SGO-T test in the differential diagnosis between pulmonary infarction and myocardial infarction a little uncertain. This seems to be particularly true if there is a large congested liver in addition to the pulmonary infarcts.

In acute pancreatitis the curve of SGO-T activity in serial determinations may resemble very closely that seen in myocardial infarction.

In liver disease the SGO-T test appears to have distinct diagnostic value. The level of this enzyme is not related to the degree of jaundice or to the commonly employed tests of liver function. While the function tests give information relating to the degree of damage to living cells, the SGO-T test appears to be related to the amount of cellular destruction taking place at the time the test is made. The data suggest that in biliary obstruction, whether due to extra- or intrahepatic bile duct obstruction, there occurs a more or less constant low-grade destruction of liver cells. In hepatitis or in the active phase of Laennec's cirrhosis, a large amount of cellular destruction is taking place as evidenced by the high levels of SGO-T seen in these diseases. These findings and impressions are in accord with those of Wroblewski and LaDue[13] and with DiRitis, Coltori, and Giusti.[14] The SGO-T test would appear to have value both in the differential diagnosis between hepatitis and obstructive jaundice and in following the course of hepatitis or active cirrhosis. In the last two diseases a rising level of SGO-T would be indicative of a worsening of the disease while a falling level would indicate improvement.

In cancer metastases to the liver the SGO-T level would appear to depend on whether the tumor is producing its effect by compression of the bile ducts or by

rapid destruction of liver cells. Examples of both types have been observed In our series. Cancer in itself does not produce SGO-T elevation.

The situation with regard to infarcts of the brain and kidneys is not entirely clear. We found a small SGO-T elevation in one patient with a cerebral vascular accident and none in two others. However, in one case of combined infarction of kidney and brain there was quite significant elevation. One other case of unproved but probable renal infarction showed only minimal elevation of SGO-T.

Our finding of a high SGO-T level in a patient with muscular dystrophy is at variance with the report of LaDue[15] who found normal values in this disease. To our knowledge our patient with paroxysmal myoglobinuria is the first to have been studied with serial SGO-T determinations. This case has been reported in detail elsewhere.[16]

Elevations of SGO-T following surgical procedures have also been noted by Lemley-Stone and associates.[17]

Data on the infants are recorded as a matter of general interest.

The findings serve to emphasize the point that elevation of serum glutamic-oxalacetic transaminase activity may be due to the destruction of many different body tissues. While assay of the blood level of this enzyme may be of great diagnostic value, particularly in coronary occlusive disease and in liver disease, it in no way relieves the physician of the necessity of interpreting the test in the light of the total clinical setting. In the differential diagnosis of myocardial infarction, for example, the test cannot be relied upon to exclude pericarditis, pulmonary infarction, or acute pancreatitis.

In certain situations the time course of the SGO-T level may be of the utmost importance in determining its diagnostic value. The prolonged elevation seen in hepatitis could not be confused with the few days of elevation seen in myocardial infarction. In other situations the height of the peak level of serial determinations may be the primary consideration, particularly in liver disease where the levels in hepatitis are likely to be several hundred units above those in biliary obstruction.

Observations in the surgical patients indicate that the SGO-T test must be interpreted cautiously in the postoperative patient because the tissue damage resulting from the operation may itself produce elevations lasting several days.

The SGO-T test as it is now performed is highly nonspecific but it is to be hoped that in the future means will be found to determine the tissue of origin of the enzyme which is producing elevation in the blood. The test would then become highly specific and of inestimably greater value than at present.

SUMMARY

1. The results of serum glutamic-oxalacetic transaminase (SGO-T) tests in 111 patients with a wide variety of disease states is reported.

2. No elevations of SGO-T were found in patients with mild benign idiopathic pericarditis, uncomplicated congestive heart failure, various forms of congenital and acquired heart disease, 2 cases of pulmonary infarction, chronic pancreatitis, quiescent nonicteric cirrhosis of the liver, congenital hemolytic jaundice, various forms of cancer, cerebral vascular accidents, pneumonia, sub-

phrenic abscess, chronic nephritis, dissecting aneurysm, diabetes, dermatomyositis, 50 per cent of postoperative patients, and 4 out of 5 newborn infants.

3. Slight elevations of SGO-T were found in rheumatic pericarditis, pulmonary infarctions with and without congestive heart failure, quiescent nonicteric cirrhosis of the liver, chronic lymphatic leukemia, one cerebral vascular accident, scleroderma, shock, diverticulitis of the colon, probable renal infarction, some postoperative patients, and 1 newborn infant.

4. Marked elevations of SGO-T were found in severe idiopathic pericarditis, preterminal shock and cyanosis, acute pancreatitis, viral hepatitis, obstructive jaundice, cirrhosis of the liver with jaundice, metastatic cancer of the liver, muscular dystrophy, paroxysmal myoglobinuria, infarcts of kidney and brain, one postoperative patient.

5. In liver disease, biliary obstruction produces levels of SGO-T ranging from 100 to 200 units, while active cell destruction as seen in hepatitis and active cirrhosis produces levels of 300 to 2,000 units.

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PULMONARY SARCOIDOSIS

A Physiopathologic Analysis

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ALTHOUGH the general character of pulmonary sarcoidosis has been amply described,[1,2] certain aspects of the disease as it affects the lung remain unclear: its unpredictable clinical course, the relationship between abnormalities in pulmonary function and the pathologic picture, and the frequent disparity between symptoms and radiologic findings.

Several very careful studies of the lung function in sarcoidosis have been published[3-10] and whenever diffusing capacity of the lung has been measured an alveolar-capillary block has been found. Almost all investigators have agreed that hyperventilation is a cardial feature of pulmonary sarcoidosis and that impairment of intrapulmonary gas distribution is less prominent than in emphysema. However, there has been some disagreement concerning the level of the residual lung volume in cases of sarcoidosis,[3,5,8,9] and the indications for the use of adrenal cortical steroid or ACTH therapy have been questioned.[9]

The residual lung volume is of basic significance in pulmonary physiology for, although its direct relation to gas exchange is slight, it reflects the architecture of the lung, perhaps better than any other currently used test. In general, patients with emphysema and pulmonary distention produced by bronchial obstructive lesions have large residual volumes whereas space-occupying lesions such as intra-alveolar or interstitial fibrosis decrease the residual volume. Reduction of total intrathoracic volume or collapse of many lung segments might also lower the residual volume.

Cases of pulmonary sarcoidosis have been reported with high,[5] normal,[6] or low[3,8,9] residual volumes. Some of the largest series have included examples of all three of these situations,[8,9] and these variable data have been correlated with other clinical and physiologic phenomena, thus forming three or more categories of pulmonary sarcoidosis. Similarly, judging by the published results, the response to cortisone or ACTH therapy has proved erratic; some patients have improved gratifyingly,[11-15] others have become worse.[9]

Observations of 23 cases of pulmonary sarcoidosis in this laboratory have indicated that the residual volume is often decreased. This reduction is not merely part of the general pattern of fibrosis but something specific to pulmonary sarcoidosis and particularly the granulomatous inflammatory process as it occurs

in the interstitial and peribronchial areas of the lung. In the present study, the data derived from these 23 cases are presented in comparison with those obtained from a general population of patients with other cardiopulmonary diseases. In addition the functional course of a patient treated for over 5 years with steroid therapy will be described.

METHODS AND MATERIAL

The following equation was used to estimate the residual volume: RV = FRC − ERV. In which: RV = residual volume in liters. FRC = functional residual capacity in liters determined by a modification of the method described by Darling, Cournand, and Richards.[16] ERV = expiratory reserve volume in liters determined by direct spirometry. The volumes are expressed in BTPS terms (body temperature, pressure, saturated with water vapor).

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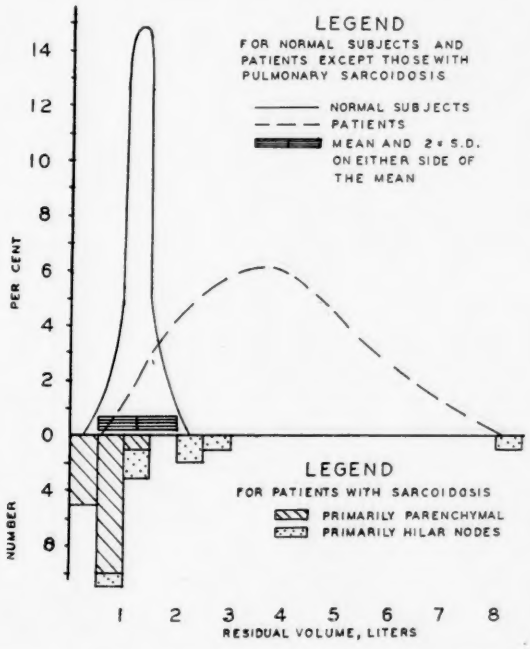

Fig. 1.—Upper portion. Distribution curves for residual lung volumes of normal subjects and the patient population of the Cardiopulmonary Laboratory. All cases in whom a diagnosis of sarcoid has been made were excluded.

Lower portion. Residual lung volumes observed in 23 patients in whom a diagnosis of pulmonary sarcoidosis had been made.

Other pulmonary function tests reported in this study were done by standard methods.

The distribution curve of normal values (Fig. 1) for this laboratory was based on 67 healthy subjects of both sexes, ages varying from 18 to 40. (The age

range of the normal group was below that of the sarcoid group.) The distribution curve (Fig. 1) for patients with all types of cardiopulmonary diseases except sarcoidosis was based on a statistical sample of patients who have been referred to the Cardiopulmonary Laboratory since it was started in 1948, or 1,062 patients altogether. Sixty-four patients with a tentative diagnosis of sarcoid were excluded before sampling. The sample consisted of 100 patients chosen by using a table of random numbers.[17]

Patients have been referred to the Cardiopulmonary Service from the following sources: the in- and outpatient services of the Grace-New Haven Community Hospital; The Woodruff Center and The Gaylord Farm Sanatorium (both chronic disease and rehabilitation hospitals); and the private practices of many physicians in the New Haven area. Thus the group constitutes a cross section of patients with chronic cardiopulmonary diseases from a large general hospital, two chronic disease hospitals, and the private medical practice of an urban community. Both sexes and all ages, races, and socioeconomic groups are represented.

The age range for the sarcoid group was 21 to 60 years. In all, 64 patients were referred with a diagnosis of Boeck's sarcoid. However, only 23 met the diagnostic criteria used by the Cardiopulmonary Service for the diagnosis of Boeck's sarcoid. These are: (1) a compatible clinical picture; (2) the elimination of all other prominent granulomatous diseases by appropriate bacteriologic examinations, skin tests, etc.; and (3) a tissue biopsy consistent with the diagnosis.

The patients have been observed for one to 6 years.

OBSERVATIONS

The range of residual volumes in the sarcoid group is low compared to the normal values for this laboratory. The mean of the normal values is 1.245 liters, and twice the standard deviation (2×0.390) on either side of the mean results in a range of 0.465 liters to 2.025 liters (Fig. 1). For contrast a distribution curve was constructed to represent all patients referred to the laboratory (excluding 64 referred with a diagnosis of sarcoid). Fig. 1 shows that this group had a range of 0.8 to 8.0 liters; well above the normal. Excluding 7 patients with sarcoid whose chest x-ray showed only hilar or mediastinal adenopathy, the remaining patients with radiologic evidence of parenchymal infiltration due to sarcoidosis had residual volumes that were lower than the normal mean, and in most cases below the lower limits of normal (Fig. 1). The cases with primarily hilar adenopathy were distributed in the range of the general patient population but, for the most part, below the mean of this group also.

Eleven patients were studied before and after inhaling sufficient bronchodilator aerosol (a racemic form of epinephrine) to produce a tremor of the hands. (One patient, T. P., was tested in this way early and late in the course of her disease). The results shown in Fig. 2 were rather unexpected in that the residual volume increased in 7 out of 12 tests (7 of 11 patients, one patient having been tested twice with no change on the second test) at the same time that the maximal breathing capacity increased. In 2 of the 3 patients in whom the residual volume decreased, the maximal breathing capacity also decreased. Thus in the present

group of patients, racemic epinephrine aerosol inhalation tended to increase residual volume, and the increase was associated with improvement in dynamic function as measured by maximal breathing capacity. The general experience of the laboratory in other types of chronic lung disease has been that bronchodilators either have no effect or decrease the residual volume.

Nine of the patients were studied repeatedly while on prolonged steroid therapy. Fig. 3 demonstrates the change of residual volume and maximal breathing capacity between the time of the patient's greatest incapacity and that of his

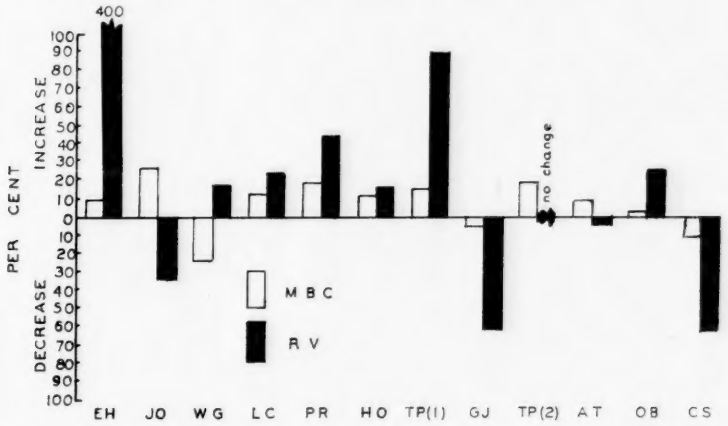

Fig. 2.—Effect on maximal breathing capacity and residual lung volume of inhaling a racemic epinephrine aerosol in 12 tests on 11 patients with pulmonary sarcoidosis. The change is expressed as per cent increase or decrease from the resting value.

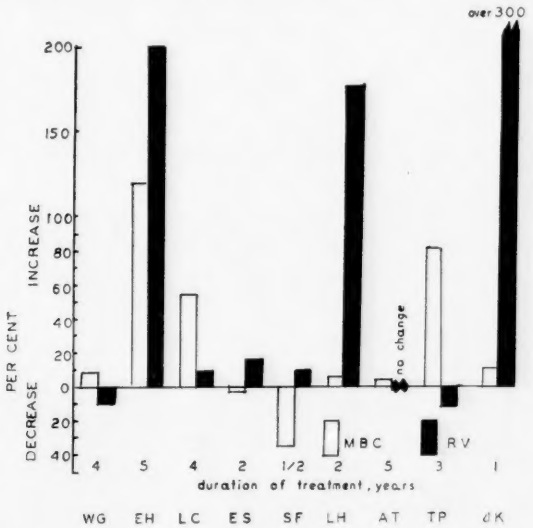

Fig. 3.—Change in maximal breathing capacity and residual lung volume after treatment with ACTH or cortisone for 6 months to 5 years in 9 patients with pulmonary sarcoidosis, expressed as per cent increase or decrease from base-line value.

optimal clinical improvement. Two patients (T. P. and J. K.) were at their best clinically before the treatment, and they became progressively worse during treatment. The other 7 patients were clinically at their best after 6 months to 5 years of treatment.

Both residual volume and maximal breathing capacity were highest when the patient was clinically at his best in 4 cases, while in 2 the residual volume dropped and the maximal breathing capacity increased. In 2 others the residual volume increased while the maximal breathing capacity dropped. There was no change in either function in one case.

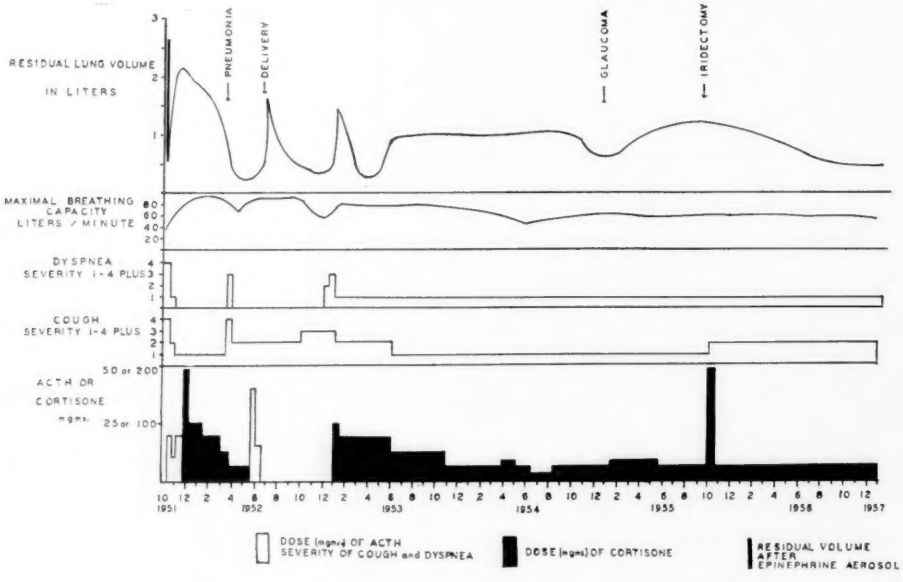

Fig. 4.—Five-year course of one patient (E.H.) on ACTH and cortisone therapy.

The clinical course of one patient (E.H.) will be described in some detail because of the long period of study and several complicating factors. When first seen this 27-year-old Negro housewife gave a 5-month history of progressive exertional dyspnea and cough productive of up to one-half cup of white sputum daily. One and one-half years prior to admission a chest x-ray, at the time of the delivery of her third child, revealed only bilateral hilar adenopathy. The admission x-ray revealed widespread confluent nodular densities throughout all lung fields. The tuberculin P.P.D. test was negative in first and second strengths. All other skin tests, sputum studies, and blood agglutination tests were negative. She had a palpable liver and spleen. Liver biopsy revealed many granulomata without necrosis consistent with the diagnosis of Boeck's sarcoid. Liver biopsy repeated after 6 weeks of ACTH and cortisone therapy showed only normal liver tissue. The course of her disease is presented in Fig. 4.

On admission dyspnea at rest and productive cough were severe. She had a very low residual volume, 0.570 liter, low maximal breathing capacity, 35 liters per minute, and high 7-minute end-tidal nitrogen level, 5.6 per cent, indicating poor intrapulmonary distribution of respiratory gases. The latter is usually seen only in very advanced cases of pulmonary sarcoidosis. Noteworthy was the observation that racemic epinephrine aerosol dramatically increased the residual volume and, to a lesser extent, the maximal breathing capacity (E. H., Figs. 2 and 4). However, after the acute effects of the aerosol had dissipated, her pulmonary function tests reverted to the base-line values. Following treatment with ACTH, and then cortisone, her residual volume, maximal breathing capacity, and intrapulmonary gas distribution approached the values found in the beginning immediately after the bronchodilator aerosol, and the residual volume was actually somewhat above normal. The change, although present by the fifth day, did not reach its maximum until after 2 weeks. Three months later the dose of cortisone was gradually reduced. Six months after starting treatment she developed a right lower lobe pneumococcal pneumonia which resolved on penicillin. In the meantime it was discovered that she was in the fifth month of pregnancy. Several weeks after recovering from pneumonia, and 9 months after the first admission, she was again admitted for a normal, full-term, spontaneous delivery of a healthy male child. She had been maintained on ACTH instead of cortisone for the 2 weeks prior to delivery. Following delivery she did not complain of exertional dyspnea, although her cough had been worse since the pneumonia. Upon discharge from the hospital, following delivery, ACTH was stopped, and inadvertently cortisone was not begun. Week by week her residual volume dropped. It reached 370 c.c. and, over a period of 3 or 4 days, she became very dyspneic. Cortisone was started again, and the dyspnea diminished as the residual volume rose to a normal level. A subsequent drop occurred in the residual volume, but after several months on a high dosage of cortisone, it rose to normal. She has never since been completely free of dyspnea, cough, or sputum, but, except for a short period in the fourth year of observation, her residual volume has been normal. She has been on a continuous cortisone regimen without evidence of hyperadrenalism. She developed glaucoma during the thirty-ninth month of observation and had a transient drop in residual volume. Diamox was administered with some relief of the glaucoma but a left iridectomy was done 9 months later. At present she has impaired vision but is able to read. In spite of mild exertional dyspnea and cough, she maintains the normal activity of a housewife with 4 children.

DISCUSSION

Sarcoidosis of the lung involves bronchial structures, alveolar septa, interstitial and vascular tissue, and all of these in varying degree. Furthermore, concomitant bronchitis, asthma, emphysema, and fibrosis of other types may occur and certainly complicate the physiologic picture as well as the response to treatment in pulmonary sarcoidosis. Finally, the repeated pneumonitis sometimes seen in sarcoid may have its own consequences as far as the clinical and physiologic picture is concerned. Hence the physiologic vagaries and numerous classifications which have been reported are not unexpected.

Since the course of any disease is often progressive in spite of therapy, deterioration in pulmonary function cannot be ascribed to a treatment failure—certainly not to treatment itself—unless sufficient controls have been used to be certain that the course would have been more satisfactory without treatment. By the same token, without sufficient controls, improvement cannot be ascribed to a specific treatment since spontaneous remissions may also occur. The disease progressed during steroid treatment in 2 of the patients reported here, but the progress appeared more rapid when treatment was discontinued. Until the disease can be experimentally produced in animals or human volunteers or until controlled observations have been made of larger numbers of patients, definitive conclusions about the response to treatment will remain unwarranted. None of the reported series including the present one contains such numbers of patients. However, some rather outstanding physiologic observations have recurred often enough in the literature on pulmonary sarcoidosis to deserve consideration.

Many reports have attested to the frequent impairment of gas exchange across the alveolar membrane in pulmonary sarcoidosis.[4,7,8,10] Most investigators of this disease have also recorded the state of hyperventilation, unusual for the apparent degree of pulmonary disability.[6,8,9,18] The low residual volume observed so frequently in the present series has been less uniformly noted.

There are three apparent means whereby the residual volume can be reduced: (1) encroachment from outside the lung as in pneumoperitoneum; (2) filling of alveolar spaces as in acute pulmonary edema, pulmonary vascular congestion, inflammatory consolidation, or fibrosis of the alveolus, alveolar septum, or interstitial tissue; (3) bronchial or bronchiolar obstruction with collapse of distal segments. Of course, in the last instance part of the reduced space would be made up by compensatory distention of surrounding segments. However, collapse of pulmonary segments would lead to increased elastic-like retraction of the lung resulting in a lower resting position of the chest wall, and a higher resting position of the diaphragms with consequent reduction in the residual volume.

Exuberant granulations of the alveolar septa could certainly fill the alveolar spaces thus reducing the residual volume. Dissipation or contraction of these granulomata with cortisone therapy could result in the increase in residual volume observed in many cases. It is difficult, however, to believe that racemic epinephrine could, in a few minutes, significantly shrink fibrotic granulomas and thereby reduce the residual volume. There are, on the other hand, some effects of epinephrine which might explain the phenomenon. First, the low-grade granulomatous inflammatory process occurring in the bronchial wall could account for sufficient mucosal swelling or bronchoconstriction to occlude some bronchi. Epinephrine reduces inflammatory reaction in the bronchopulmonary system generally and could thus allow the collapsed segments to be ventilated again. This same anti-inflammatory effect could cause fresh, nonfibrotic granulomata in the alveolar septa to shrink. Another less likely explanation is that epinephrine might open up the channels of collateral respiration, which appear to vary in patency; they close in response to histamine.[19] The low residual volumes have usually been observed when the patient was clinically at his worst. This suggests that it is a function of the degree of activity of the disease process and supports the

concept of a granulomatous inflammatory reaction rather than fibrosis. In contrast, patients with extensive radiologic involvement of the lung but with few clinical symptoms have been found to have normal or greater than normal residual volumes. In all probability the pulmonary symptoms reflect an active state of the disease with a low-grade inflammatory reaction rather than fibrosis. Treatment, then, may relieve the inflammatory state, thus ameliorating the symptoms. In some cases (i.e., E. H.) adequate treatment may cause at least temporary disappearance of the granulomas (liver biopsies). This probably occurs only in early, acute disease.

Cortisone therapy does not always reverse the disease process; in fact, 2 of the 9 patients reported here who were treated with ACTH or cortisone progressed to fatal termination in spite of this treatment. However, in the other treated cases the status of the patient appeared to improve and the improvement correlated very well with the dosage of cortisone. As in other diseases, a particular treatment which is generally effective may fail to benefit some patients. In our series, the 2 patients who died had clinical and autopsy evidence of rapidly progressing disease. We believe that those who did well on therapy improved by virtue of the anti-inflammatory effect of the treatment. The low residual volume observed during stages of exacerbation followed by increase during improvement supports the concept that pulmonary insufficiency in sarcoidosis is often the result of low-grade inflammation as well as fibrosis. Inflammation would better explain the hyperventilation often observed since the latter is not seen to so great an extent in other types of fibrosis. Hyperventilation does occur frequently in inflammatory diseases such as acute rheumatic fever and acute periarteritis. Inflammation also could result in the observed alveolar-capillary block.

Thus much of the physiologic impairment in sarcoid could be due to low-grade inflammatory response with its proliferative and exudative components rather than to fibrosis. The end result of pulmonary sarcoidosis is, of course, extensive fibrosis which unquestionably results in greatly impaired function. This may be, however, only a late phenomenon.

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SUMMARY

1. Analysis has been made of the pulmonary function tests and clinical courses of 23 patients with pulmonary sarcoidosis. In 9 of the 23 patients the severity of symptoms warranted treatment with ACTH or cortisone over periods ranging from 1 to 6 years; improvement occurred in 7 of the 9 patients who were so treated.

2. Remarkably low residual lung volumes were found in 19 cases. Both racemic epinephrine aerosol and steroid therapy increased the abnormally low residual volumes toward normal, and the increase correlated well with clinical improvement. This phenomenon together with the hyperventilation also observed seemed better explained by the inflammatory character of the sarcoid granuloma than by fibrosis. Resolution of the inflammation is enhanced by ACTH or cortisone and, temporarily, by racemic epinephrine aerosol inhalation.

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POSTURAL BLOOD PRESSURE CHANGES IN THE ELDERLY

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ORTHOSTATIC hypotension is attracting increasing attention since it has been found to be an important side effect of sympathectomy, of ganglionic blocking agents, and of some of the so-called ataractic drugs. A study of the response of the aged to an orthostatic tolerance test seemed worth while because anatomic evidence indicates that the autonomic ganglion cells intimately concerned with the mechanism of the response of the circulation to such stimuli as standing suffer degeneration with aging. Thus there is a material reduction in the number of effective vasomotor and cardioaccelerator fibers with aging which might result in a delayed and ineffective response to standing.[1] Further, a variety of symptoms which have been attributed to orthostatic hypotension in younger patients are common in the elderly. These include dizziness, headache, syncope, faintness, weakness, lack of mental concentration, and dimness or blurring of vision. Accentuation of these symptoms on arising in the morning, with improvement during the course of the day and on lying down, have also been attributed to orthostatic blood pressure changes. To determine the validity of these suggested relationships, a group of older men and women have been subjected to a standard test for orthostatic hypotension.

The drastic results of tilting experiments have led Eichna[2] to suggest "that if healthy young men can develop circulatory failure while erect after exercise, one may guess that similar circulatory changes are not only more likely in older age groups but that they may be more readily induced, more severe in their manifestations, and capable of serious consequences."

Finally, sudden hypotension of any origin may result in tissue damage in the presence of narrowed arteries, either in the heart, the brain, or the kidneys.

MATERIALS AND METHODS

Two hundred and fifty ambulatory residents of the Home for Aged and Infirm Hebrews of New York were given an orthostatic tolerance test at the time of their annual examinations. The test used was that of the Civil Aeronautics Authority, described by Foley.[3] The subject lies in the dorsal recumbent position with the cuff on the arm for at least five minutes, and blood pressures are recorded at one-minute intervals until two similar readings are obtained. The subject then stands in an erect position without leaning on anything for three minutes.

We recorded the blood pressures immediately upon standing, at 90 seconds, and then at 180 seconds. At the time of testing, only those symptoms spontaneously evoked from the subject were noted in an attempt to avoid the factor of individual suggestibility. Standard conditions were observed in the taking of the blood pressure as to cuff type and placement, type of machine employed (mercury), time of day, room temperature, and type of stethoscope. The systolic pressure was noted at the first audible sound, the diastolic at the complete cessation of sound.

The attached questionnaire of symptoms commonly attributed to orthostatic fall in pressure and related characteristics was completed by each patient tested several months later (Table I), without any mention being made of any connection between the two procedures. At the time of analysis, symptoms due to associated known disease, such as dyspnea from cardiac failure or pulmonary disease, were excluded.

TABLE I. QUESTIONNAIRE-SYMPTOMATOLOGY

I. Do you suffer from any of the following:	(Encircle *Yes* or *No*)	
A. Dizziness	Yes	No
B. Headaches	Yes	No
C. Faintness or fainting spells	Yes	No
D. Weakness	Yes	No
E. Shortness of breath	Yes	No
II. Are these symptoms worse in the morning?	Yes	No
III. Are these symptoms worse on getting out of bed?	Yes	No
IV. Do these symptoms get better if you lie down?	Yes	No
V. Do these symptoms get better during the latter part of the day?	Yes	No
VI. Are any medications taken for these symptoms?	Yes	No
A. Name of medication		
B. Symptom for which taken		

Since none of the subjects met the stringent standards of the Civil Aeronautics Authority for an abnormal response, i.e., a fall to 90/54 or less, we analyzed the series in accordance with the standards set for normals by Akesson, quoted by Nylin and Levander,[4] in a similar test, namely, after standing for 3 to 5 minutes the systolic pressure does not fall more than 20 mm. and the diastolic rises slightly or falls not more than 5 mm.

RESULTS

In Table II, an analysis is made of the total group with regard to age and sex. The group of 250 residents included 85 males and 165 females ranging in age from 61 to 91 years.

In Table III the range and degree of blood pressure change on standing is detailed for the entire group. While appreciable falls in diastolic pressure of more than 20 mm. were rare and falls to 90/54 or below did not occur, systolic falls of more than 20 mm. occurred in a little over 10 per cent of the group with

4 per cent exceeding 40 mm.; 24 per cent exceeded the diastolic limit of 5 mm. fall. Cases whose falls exceeded both systolic and diastolic limits of normality were 8 per cent of the entire group. Moderate rises in diastolic pressure were common, occurring in almost 23 per cent of the group.

TABLE II. AGE RANGE AND SEX DISTRIBUTION OF 250 AMBULATORY AGED PATIENTS

Number of Patients		250
Age range	61-70	32
	71-80	140
	81-91	78
Sex	Male	85
	Female	165

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TABLE III. ORTHOSTATIC CHANGE IN BLOOD PRESSURE IN AGED PATIENTS

	TOTAL
Number of patients	250
A. Systolic fall on standing exceeds 20 mm. Hg	28
B. Diastolic fall on standing exceeds 5 mm. Hg	60
C. Patients with A plus B	20
D. Systolic fall from 40 to 62 mm.	10
E. Fall to 90/54 or below on standing	0
F. Diastolic fall from 20 to 40 mm.	1
G. Systolic rise on standing exceeds 20 mm. Hg	9
H. Diastolic rise on standing exceeds 5 mm. Hg	57
I. Patients with G plus H	3
J. Systolic rise from 40 to 46 mm.	1
K. Diastolic rise from 20 to 30 mm.	4

TABLE IV. RELATION OF SYMPTOMS TO ORTHOSTATIC CHARACTERISTICS, FALL IN BLOOD PRESSURE AND RESTING BLOOD PRESSURE

SYMPTOM	NO. PATIENTS	NO. WITH ASSOCIATED SO-CALLED ORTHOSTATIC SYMPTOMS*	NO. WITH BLOOD PRESSURE FALL OVER 20 SYSTOLIC	NO. WITH RESTING BLOOD PRESSURE OVER 170/100
Headaches	52	45	4	12
Dizziness	48	40	9	8
Fainting spells and fainting	14	13	6	4
Weakness	51	46	5	7
Dyspnea (not related) to heart failure or pulmonary disease	32	30	4	8

*Positive answers to questions II, III, IV, and V of questionnaire in Table I.

In Table IV, the individual symptoms studied are correlated with the incidence in each group of systolic falls of over 20 mm. Hg on standing and with

elevation of the blood pressure. Headaches, dizziness, and weakness predominated with dyspnea next in frequency. A low incidence of faintness and fainting spells was recorded. So-called orthostatic symptoms were common in all groups. Systolic falls over 20 mm. on standing and elevation of the resting blood pressure over 170/100 were uncommonly associated with each symptom. Only faintness and fainting spells were associated with a definite systolic fall on standing in an appreciable number of patients.

In Table V, an outline is made of some possible causative factors discovered in the group with systolic falls over 20 mm. on standing. Moderate to severe varicose veins and old thrombophlebitis predominated. The incidence of severe varicose veins and thrombophlebitis in this group was more than double that found in a group of individuals without a significant fall in blood pressure on standing. Eleven complained of none of the symptoms studied.

TABLE V. ANALYSIS OF PATIENTS WITH SYSTOLIC FALL ON STANDING BETWEEN 20 AND 62 MM.

1.	Number of patients	28
	Males 9	
	Females 19	
2.	One or more "etiologic" factors present	21
	absent	7
3.	"Etiologic" factors—moderate to severe:	
	Varicose veins	14
	Thrombophlebitis	5
	Diabetes mellitus	3
	Diabetes with neuritis	1
	Previous cerebrovascular accident	3
	Severe peripheral vascular disease with occlusions and/or intermittent claudication	3
	Severe Parkinsonism	1
	Severe anemia	1
	Hematomyelia (due to Dicumarol therapy)	1

In Table VI, an analysis is made of the resting blood and pulse pressures in the group by sex. It can be seen that while normotensive pressures were few in number in both sexes, elevations over 170/100 and 200/100 were predominant among the women. Similarly, while normal pulse pressures were infrequent among both sexes, wide pulse pressures were more frequent among the women.

DISCUSSION

Studies of many investigators have shown that on standing there is an immediate shift of blood from the upper to the lower parts of the body with a resultant pooling of blood in the lower extremities and to a lesser extent in the splanchnic bed. The venous return and cardiac output are consequently decreased. In the normal there are almost instantaneous compensatory adjustments. On the venous side there is increased pumping and massaging action of the muscles, a sucking of the blood upwards by the increased negative pressure in the thorax,

TABLE VI. DISTRIBUTION OF BLOOD PRESSURES IN 250 AMBULATORY AGED PATIENTS

	MALE	FEMALE	TOTAL
Over 200/100	5	21	26
170/100-to 200/100	9	29	38
140/80-to 170/100	55	99	154
Less than 140/80	16	16	32
Total	85	165	250

DISTRIBUTION OF PULSE PRESSURES IN 250 AMBULATORY AGED PATIENTS

101-150	11	28	39
61-100	47	112	159
Less than 60	27	25	52
Total	85	165	250

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and probably active vasoconstriction of the veins in the lower extremities mediated through the carotid sinus and aortic body mechanisms. On the arterial side the carotid sinus and aortic body reflex mechanisms cause an increase in heart rate and generalized vasoconstriction. The subject has been very well covered by Nylin and Levander.[4]

Abnormal responses sufficient to cause appreciable falls in blood pressure and symptoms have been classified into two predominant groups, though it must be appreciated that there is considerable overlapping between these groups and that some cases show some of the characteristics of both.

The "asympathotonic," "postural hypotension," or "hypodynamic regulatory disturbance" type is rare and dramatic and has attracted most of the attention of the literature. Only about 100 cases have been reported. On standing, a rapid fall in both systolic and diastolic pressure to very low levels approaching zero occurs, with little or no change in pulse rate together with faintness, dizziness, vertigo, etc., or even loss of consciousness. It is considered a disease of the central nervous system associated at times with such conditions as diabetic neuritis, tabes, syringomyelia, hematomyelia, and arteriosclerotic brain disease. The severe reaction to standing is attributed to an absence of reflex response of both the arterial and venous mechanisms, as described previously.

In spite of the advanced age of our population and the relative prevalence of appropriate etiologic factors such as arteriosclerotic brain disease, there were no such cases in our group. This may be attributed to the over-all rarity of this condition.

The most common type of abnormal response to standing has been termed "sympathotonic," "arterial orthostatic anemia," or "hypotonic regulatory disturbance." On standing, there is a fall in systolic pressure with no change or a rise in diastolic pressure together with an increase in pulse rate. The fall in systolic pressure is attributed to failure of the venous compensatory mechanisms with resultant pooling of blood in the lower extremities, diminished venous return,

and cardiac output. The intact arterial reflex compensatory mechanisms cause a vigorous arteriolar vasoconstriction and tachycardia which maintain the diastolic pressure. It is most commonly seen in association with pregnancy, extensive varicose veins or angiomata, marked anemia, and on arising from bed after prolonged and debilitating illnesses.

Ten of our 28 patients with falls of more than 20 mm. systolic on standing fell into the above physiologic category. Three complained of none of the symptoms studied, including one with a systolic fall of 60 mm. on standing, one of the 2 cases in the entire series with a fall of such magnitude. Seven had one or more possible etiologic factors such as moderate to severe varicose veins in 5, thrombophlebitis in 2, severe peripheral vascular disease in 1, diabetic neuritis in 1, severe anemia in 1, and hematomyelia in 1. In only 2 did actual symptoms come to the attention of the examining physician at the time of testing. In the patient with hematomyelia and neurologic changes secondary to previous Dicumarol therapy, dizziness was complained of, with a fall of 36 systolic and 2 diastolic; in another, dizziness also was complained of with a fall of 40 systolic and 2 diastolic in a case with definite diabetic neuritis. The results were duplicated on repeated trials in both patients.

The remaining 18 patients with a systolic fall on standing differed from the above 10 in that there was a diastolic fall up to 20 mm. which could be attributed to a partial failure of arteriolar vasoconstriction. This has been ascribed to diminished sensitivity of the carotid sinus to hydrostatic pressure in the aged. Eight complained of none of the symptoms studied. Fourteen had one or more "etiologic" factors such as moderate to severe varicose veins in 9, thrombophlebitis in 3, previous cerebrovascular accidents in 3, diabetes mellitus in 3, severe peripheral vascular disease in 2, and severe Parkinsonism in 1. In none were symptoms complained of at the time of testing.

It is interesting to note that in the 1 case in the entire series in whom a fall of more than 20 mm. diastolic pressure occurred, an individual with a fall of 0 systolic and 40 mm. diastolic, there were no symptoms or obvious etiologic factors.

While extreme falls in blood pressure on standing did not occur in this group, moderate falls in systolic pressure occurred in over 10 per cent. This may be due to excess pooling of venous blood in varicose veins resulting in diminished venous return and lessened cardiac output. Few complained of symptoms at the time of testing and 50 per cent were asymptomatic at all times. The absence of symptoms may be attributed in part to the lessened appreciation of sensation in general in the aged, which has been noted in the aged with silent myocardial infarction and other conditions,[6] and in part to the widespread incidence of memory impairment in the aged.

Table III also reveals that the aged show a high incidence (almost 25 per cent of the series) of abnormal falls in diastolic pressure on standing. This may be attributed to the well-known fact that the aged require more time to adjust to physiologic stresses in general[7] and to diminished carotid sinus sensitivity to hydrostatic pressure in particular,[5] with resultant partial failure of the compensatory vasoconstrictor and cardioaccelerator mechanisms.

The fact that more drastic responses were not obtained as predicted by Eichna[2] may be explained by the fact that the stress of this test is far less severe than that elicited by the tilting type experiment he used.

The rises in blood pressure on standing may be attributed to an "overshoot" of the compensatory arteriolar vasoconstrictor reflexes.

Statistics as to the frequency or degree of blood pressure change on standing in the aged are rare in the literature. Droller and Pemberton[8] in a series of 476 aged living at home found five men and ten women all of whom developed profound fall in pressure after 2 minutes of standing with loss of balance and falling. The range of systolic fall was from 0 to 50 systolic, 0 to 90 diastolic in 13 patients, and in 2 patients the pressure was not obtainable on standing. The latter 2 would presumably be asympathotonic cases. The former 13 roughly correspond to our patients but differ in the constant finding of immediate, severe, and marked findings.

The individual symptoms (Table IV), with the possible exception of faintness and fainting spells, show no relationship to orthostatism despite a very high incidence of so-called orthostatic characteristics. It may well be that in the aged, cerebral arteriosclerosis far outweighs orthostatism or resting hypertension as a causative factor for such complaints. Droller, Pemberton, and Roseman[9] found a similar lack of relationship between the height of the resting systolic or diastolic blood pressure and vertigo and tinnitus.

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SUMMARY

1. In a group of 250 ambulatory aged persons, marked falls in systolic blood pressure (more than 62 mm. Hg) or of diastolic blood pressure (more than 40 mm. Hg) were not found on change from the recumbent to the standing position. In no case did the level on standing fall to below 90 mm. Hg systolic over 54 mm. Hg diastolic.

2. Mild but abnormal falls of the systolic and diastolic blood pressure levels on standing were frequent.

3. A high incidence of marked varicose veins and thrombophlebitis was found in the group with falls of more than 20 mm. in systolic pressure on standing.

4. Symptoms such as weakness, dizziness, and headaches, commonly attributed to orthostatic variations of the blood pressure, were frequent but had no relationship to the occurrence of appreciable falls in blood pressure on standing or to the occurrence of elevated resting blood pressure.

5. Symptoms such as dizziness and headaches, commonly attributed to hypertension, were frequent but had no relationship to the resting level of the blood pressures.

6. The lack of correlation between the symptoms studied here, which are commonly attributed either to hypertension or to orthostatic changes in the blood pressure, and the actual physical findings in our series emphasize the need for caution in the interpretation and explanation of untoward subjective sensations in older patients.

We wish to thank Dr. Ernst Elias, Dr. Adolphe Metz, Dr. Arthur Arndt, Dr. Katherine Stein, Dr. Moses Schiffman, Dr. Melanie Roth, Dr. Julius Goldstein, and Dr. Alfred Bornstein, members of the Resident Physician Staff at the Home for Aged and Infirm Hebrews, for their invaluable aid in this study.

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A HOME CARE REHABILITATION PROGRAM FOR EX-URBAN COMMUNITIES

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INTRODUCTION

THIS paper describes a pilot project which provides a home care rehabilitation service to homebound patients in a semirural area. The project is but a few months old; at least two years will be needed before results can be measured. Nevertheless, the problem which the project seeks to solve is a matter of public concern. Hence, it seems useful to describe the project in the hope that interest may be further focused on the problem.

THE PROBLEM AND THE POTENTIAL RESOURCES

The handicapped patient, homebound by a chronic disease such as arthritis, frequently requires medical, nursing, rehabilitation, and social services at home. A big impetus to the movement for home care services to meet such needs came from the Montefiore Hospital Home Care Program in New York City.[1,2] This form of home care permits the patient's earlier discharge from the hospital and avoids prolonged, expensive institutionalization; it also frees hospital beds for other patients. The patient benefits by returning to his home and to at least partial resumption of household and social activities as soon as possible, while continuing to receive the hospital's medical and other care. Such a home care program, therefore, provides an important service to the chronic disease patient.

The postwar growth of suburban living—the introduction of "bedroom" or "commuter" communities into semirural areas surrounding major cities—has brought in its train a new need for home care. This population growth, plus the increasing incidence of chronic diseases, presents these communities with a gradually cumulating problem of homebound patients who can no longer perform many of the essential activities of daily living. In these areas, responsibility for the homebound patient's medical care is unlikely to center in the community hospital; rather, it remains almost entirely in the hands of the family doctor. Yet the average family physician, trained to handle the traditional medical problems, is not equipped to direct rehabilitation techniques; comprehensive rehabilitation services, moreover, are slow to start in these areas. Hence, there

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is great need to adapt and modify the home care rehabilitation pattern to serve the average suburban-rural community now housing a large and expanding segment of our population.

Though lacking home care services of the type described above, most semi-rural areas do have resources which, properly coordinated, might substitute for them, without requiring a large general hospital as the central directing force.

THE PILOT PROJECT—BACKGROUND AND PURPOSE

Growing out of four years' experience in providing physical therapy to urban homebound arthritics (in cooperation with visiting nurse agencies),[3] a new project has lately been started in northern Westchester. Rooted in established community agencies, this project provides home care and rehabilitation to the homebound patient.

The project's purposes are: to extend rehabilitation to suburban and rural homebound arthritis patients; to demonstrate what a teamwork approach can do in helping such patients to expand their activities of daily living; and to highlight the potentials of existing rural and suburban agencies for rendering rehabilitation service to all their homebound patients, regardless of diagnosis.

RESOURCES, SKILLS, AND TOOLS

The northern Westchester project centers in the family physicians, the District Nursing Association (the DNA) to which they refer patients, and in the full-time physical therapist added to the DNA's staff for the project. The continuing counsel of an experienced physiatrist from the city, and stimulus, planning, and funds are obtained from the Arthritis and Rheumatism Foundation's New York State Chapter. The cooperation of other local agencies, already working with the DNA in certain aspects of its program—Family Service of Westchester, Inc., and the county's Department of Health—were also enlisted.

Northern Westchester was selected as the project's location because of its ex-urban setting. The DNA was chosen, first, because it is a well-established agency caring for the homebound; second, because it had a case load of homebound arthritis patients many of whom needed rehabilitation (as did patients with a variety of other diagnoses); and, third, because it enjoys the cooperation of official and voluntary agencies in the community.

METHODS OF OPERATION

Initially, the project's physical therapist and the DNA director review all the case records to identify patients (whether arthritic or not) who might profit from rehabilitation. Next, each patient's physician is called to explain the new rehabilitation program, and permission is requested for the therapist to visit the patient. If permission is granted, the therapist visits the patient and makes an evaluation of the patient's joint mobility, muscle strength, and present capabilities as regards self-care activities. He then conveys this information to the family

physician either in person or by phone. The family physician and the therapist arrive at a suitable rehabilitation goal commensurate with the patient's capabilities, and clearance is obtained from the physician for the inception of a program to attain that goal.

The therapist and nurse then visit the patient together. The therapist demonstrates the exercises to the nurse; he identifies for her the activities of daily living in which the patient is handicapped but which he can learn to master again; and shows her how he may be assisted toward their renewed performance. Self-help devices are arranged for when needed. New skills in handling himself, e. g., in moving from bed to chair, are taught to the patient. Environmental changes (e.g., lighter household equipment) may be needed. Thus, the therapist trains the nurse to help the patient re-master the activities of daily living through strengthening weakened muscles, teaching new skills of motion, and identifying and making appropriate environmental changes. The physical therapist and nurse visit the patient together until the nurse, gaining confidence through practice, gradually takes over responsibility. The therapist keeps in touch with the nurse through conferences and revisits the patients at intervals to check on progress. As the nurse takes over, the therapist is freed to pick up new cases.

In planning a patient's regimen, goals are set consonant with his disease, disability, and apparent drive. The cornerstone of progress is the relation established between the patient and his family, on one hand, and the nurse and therapist on the other, as the latter must instill in the patient the confidence that he can help himself (with his family's cooperation) to reconquer lost areas of activity.

Throughout, the patient's medical supervision remains with his family physician whom the therapist consults frequently. While the therapist may suggest exercises, activities, or self-help devices to the doctor, the latter's over-all responsibility for the patient is always clear.

MONTHLY CONFERENCES AND THE ROLE OF THE PHYSIATRIST

Monthly case conferences are the integrating factor of the project. Participants include: the physical therapist; the DNA's director and nursing staff; the county public health nurses and nutritionist; the social worker from Family Service of Westchester; the physicians who refer patients to the DNA; the consultant physiatrist; and the medical director of the Foundation's New York State Chapter.

A case history is presented by the nurse in charge. The therapist discusses the patient's disability, the regimen approved by his doctor, and the stage-by-stage goals toward which this regimen is aimed. The referring physician points up the medical aspects of the case. Problems such as the patient's reaction to therapy, his motivation, his family's attitude, his housing and surroundings, diet, and need for appliances, are brought out, and solutions are discussed. The skills of each participant are called upon. If a major problem appears to lie in the patient's family relationships, the social worker is asked to suggest avenues of approach. The county nutritionist is called upon in cases where diet proves a problem. Environmental factors such as the height of bed or chair or the need for devices or orthopedic equipment are discussed and related to the family's

ability to solve them. The Chapter's Special Services Fund may be used to pay for equipment not otherwise obtainable. After full discussion, the further course of treatment and subsequent goals are set.

The consultant physiatrist functions in the role of a general consultant in rehabilitation. As such, he is responsible for the formation of proper rehabilitation concepts and attitudes within the group along with the education of the group in the application of specific rehabilitation techniques. The clinical material presented at the monthly conferences is utilized by him both in teaching concept and technique and in evaluating the therapeutic effectiveness of the group.

It should be noted that the consultant physiatrist does not directly treat patients. Rather, he guides and counsels in assessing a patient's potential for rehabilitation, in setting goals, in developing appropriate means for attaining goals, and in correlating with the patient's physician the impact of the rehabilitation program on the patient's general medical picture.

The physiatrist also contributes by establishing a realistic frame of reference both for the project and for the individual patient. His counsel is needed in revising a patient's goals, in deciding when he has made maximum progress, or when his case should be closed.

The physiatrist's experience is an essential measuring rod. His perspective and judgment encourage nurses and therapist in undertaking difficult cases and in accepting the moderate or even slight improvements achieved by certain patients. Thus he performs a most important function for the project—developing in all participants a sound understanding of the potentials and limitations of rehabilitation in the care of the homebound.

MODEST GOALS

As might be expected, certain problems have developed in the project's early stages, and solutions are being sketched out. At the start, some nurses are timid, reluctant, or unable to recognize the handicapped patient's potentials. Realistic, easily attainable goals—even though they mean very slight improvement for the patient—are important in educating and encouraging the nurse, and in enlisting the patient's cooperation. In working towards a series of short-term goals, the nurse develops confidence in the idea of rehabilitation and its techniques and in the physical therapist as a teacher and ally who enlarges her role and responsibility. Once a patient has extended her range of motion enough to comb her own hair, the nurse's confidence is expanded so that she can undertake the work toward a second, more difficult goal.

Similarly, the attainment of a short-term goal stimulates the timid patient. And his family, relieved, perhaps of the chore of dressing him, may also become more receptive to suggestions for altered care of the patient, expanded social activities, or other advisable modifications in the patient's situation.

COMMUNITY PARTICIPATION

By centering the project in the local visiting nurse agency, the community's potential interest and support are aroused. Referrals specifically for rehabilita-

tion are beginning to be received from local physicians; the community hospital has invited the Chapter's medical director to discuss arthritis with their medical staff; the DNA's auxiliary has organized a sewing project to make the sandbags needed in traction; and a retired carpenter has volunteered to make and alter self-help devices needed by patients.

ORGANIZATIONAL STRUCTURES OF HOME CARE PROGRAMS—CITY AND EX-URBAN

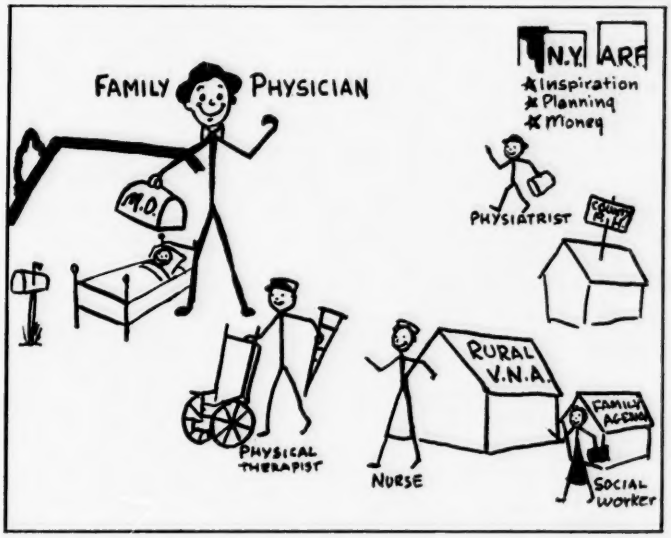

Fig. 1*A*.—Demonstration of Home Care in Ex-urban Setting. The patient's family physician is incorporated in the program. All other services, including administration, are channeled through the local V.N.A.

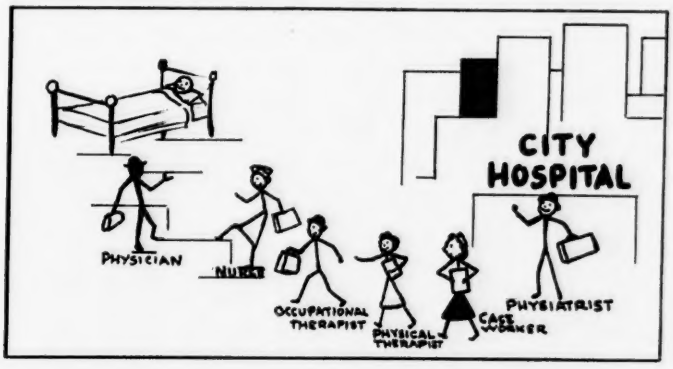

Fig. 1*B*.—Home Care Program in Large City. The physician attending the patient, all other services, and the administration of the program stem from the general hospital.

CONCLUSION

As noted earlier, this paper must be confined to discussing the techniques used in starting a new form of home care service based, not on a large general hospital, but rather on local agencies in an ex-urban community. The project is young and results cannot be anticipated for some time. However, progress is satisfactory and, indeed, encouraging.

It would appear that this type of program is capable of development in many of the ex-urban areas in this country which already have established agencies caring for their homebound. By enlisting the participation of such an agency, by coordinating all other local skills, and by adding essential technical specialists (recruited in so far as possible from the community itself) such a scheme can help the local home care agency to make modern rehabilitation techniques available to the homebound patient and to the practicing physician, techniques which, in fact, might also serve ambulatory patients in need of rehabilitation.

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THE PREVALENCE OF DISEASES OF THE HEART IN AN URBAN CENTER AS ESTIMATED FROM MEDICAL EXAMINATION OF A PROBABILITY SAMPLE

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WITH the growing recognition in the past few decades that diseases of the heart constitute one of the most important individual and public health problems, there has been an increase in the tempo of research focused on measurement of the incidence and prevalence of these diseases, assessment of their etiology, and evaluation of the effects of programs of management. While many estimates of the frequency of heart disease have been made from analysis of death certificates, morbidity surveys, and studies in cardiac clinics and rehabilitation centers, there have been few, if any, estimates based on studies involving physical examination of a cross section of the total population living in a region.

This paper reports the methods and findings of a recently completed study conducted in the Arsenal Health District of Pittsburgh. One of the objectives of the study was the estimation of the frequency of diseases of the heart among the persons 15 years of age or older residing in the district. The study area, comprising twenty-two of the 194 census tracts of the city, is an industrial and residential district stretching along the south bank of the Allegheny River in the heart of the city having a population of approximately 80,000 persons.

METHODS

Since estimates of the prevalence or incidence of various disease conditions in general population groups are becoming increasingly important and studies to produce such estimates are likely to be more frequently undertaken in the days ahead, the methods employed in this study and the difficulties encountered will be covered in some detail. Hopefully, this explanation may prove useful to other investigators facing similar problems.

At the beginning of this investigation a household survey of health conditions in the district had been completed. The full details of the methods employed in the household survey have been previously recorded.[2,4]

In summary, a sample of approximately 3,000 of the 23,000 households in the study area was selected by methods which gave each of the 23,000 households an equal chance of inclusion in the sample. An interview was conducted at each sample household during July of 1952. Health facts were elicited during the interview concerning the person furnishing the information and all other persons residing with him. Any adult person found at home at the time of the call was eligible to provide the information.

The information from the household interview permitted the subdivision of the 7,130 household residents enumerated in the survey into relatively homogeneous subgroups with respect to age, sex, reported presence or absence of heart disease, and 10 symptoms frequently accompanying diseases of the heart. A summary of the number of persons among the 7,130 in each of the 12 subgroups or strata[3] is included in the appendix table.

In the second phase of this work a sample of the 7,130 persons 15 years of age or older enumerated in the household survey was selected for personal interview in their homes and physical examination at the study clinic. The numbers chosen from each stratum for the heart study sample are recorded in column (3) of the appendix table. The selected individuals were chosen at random from all the persons present in each stratum. It will be noted that the rates of sampling varied from 100 per cent in the four strata in group A to as low as 2.7 per cent in one of the strata in group C. In general, the choice of these rates will vary with the objectives of a particular study. In the present instance the choice was a compromise between the rates which would lead to the most precise estimation of over-all prevalence of diseases of the heart from the examination data and the rates which would be most appropriate for studying the relationship of diseases of the heart to problems of finding and holding a job in various age-sex groups.

The 721 persons included in the sample were scheduled for personal interview by lay personnel beginning late in 1953. In addition to demographic data the questionnaire included direct questions about a history of heart trouble and 14 other related diseases and conditions and detailed questions on other conditions frequently symptomatic of heart disease. Times of onset of the various reported conditions were established, and the medical care experience and physician diagnosis were also ascertained. Of the 721 selected persons 518 were interviewed. Thirty-two of the sample persons had died in the interim since the household survey, and an additional 171 persons had moved from the study area, were institutionalized, refused to cooperate, or were otherwise unavailable for interview. Thus an immediate loss of 28 per cent of the selected sample was encountered.

Each interviewed person was invited to visit the clinic for a physical examination. The appointment time and arrangements for transportation were made during the interview. Only 386 of the 518 interviewed persons could be induced to accept the invitation. The 386 examined persons constitute 53.5 per cent of the originally selected sample.

The examination procedure consisted of: (1) a medical history and physical examination with particular attention to the cardiac system made by one of us (J. T.) together with a 14 × 17 roentgenogram of the chest in posteroanterior position and a 12 lead electrocardiogram; (2) a review of all the recorded findings on each of the 386 examined persons by one or more members of the group of eleven consultants in cardiology* participating in the study; and (3)

*These include the following physicians all holding appointments in the School of Medicine, University of Pittsburgh: C. R. Bauersfield, E. A. Brethauer, C. A. Clarke, E. F. Cosgrove, E. L. Forsyth, R. K. Horn, R. Lewis, R. H. Newton, G. J. Rhodes, P. M. Rike, and D. M. Wilkins. To all of them we owe a debt of gratitude for their willing contribution to this study.

a re-examination of those persons whose recorded findings suggested to the participating cardiologists a need for a more detailed examination. The examination by the cardiologists resulted in repeated electrocardiograms on five persons, fluoroscopic examination on twelve, and an x-ray kymograph of the heart on one person.

A total of 179 persons were scheduled for a second examination, however, 18 refused the invitation so that 161 persons were re-examined by the consulting cardiologist. The diagnosis of heart disease was based on the definitions of the New York Heart Association.[5] Each diagnosis of cardiac disease was made jointly by a group of at least three of the cardiologists. As an indication of those signs and symptoms which were judged significant in the diagnostic procedure, we may record that, with two exceptions, each person classified as having heart disease exhibited either one or more of the findings in Group I below, or two or more of the findings in Group II. The final diagnosis of heart disease in each case, while considering the signs and symptoms below, depended upon the judgment of the cardiologists based on all the relevant findings in the case including the blood pressure.

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Group I

a. Definite history of angina pectoris
b. Diastolic cardiac murmur
c. Grade III or IV systolic cardiac murmur
d. X-ray evidence of generalized cardiac enlargement based on prediction table for average normal transverse diameter of the heart silhouette on the 6 foot posteroanterior teleroentgenogram, or x-ray evidence of definite left ventricular enlargement based on the heart silhouette on the 6 foot posteroanterior and/or oblique teleroentgenogram and/or fluoroscopy

ECG evidence of:

e. Prolonged P-R interval over 0.21 second
f. Q more than 25 per cent of succeeding R except in AV_r and V_1.
g. QRS duration 0.12 second or more
h. Tall and/or broad R′ with delayed intrinsicoid deflection in $V_{1\text{-}2}$, QRS more than 0.08 second
j. Broad R or R+R′ without Q in $V_{5\text{-}6}$ or with very large QRS $V_{1\text{-}2}$, with or without inverted T
k. Auricular fibrillation or flutter-fibrillation
l. Numerous ventricular premature beats, occurring in all leads and especially if coupled

Group II

a. History of heart disease, especially of myocardial infarction
b. Grade I or II systolic cardiac murmur
c. Toxic goiter or hypothyroidism
d. X-ray evidence of slight left ventricular enlargement
e. QRS duration of 0.10 − 0.119 seconds
f. R_{V5} or $R_{V6} + S_{V1}$ more than 35 mm. with delayed intrinsicoid deflection
g. Paroxysmal tachycardia
h. Low voltage throughout all leads
j. Sagging ST, inverted T in L_2, L_3, aV_F, and sagging ST with isoelectric T in aV_L and V_5

Among the 161 re-examined persons 113 cases of cardiac disease were diagnosed, 45 persons were classified as having no heart disease, and 3 were classified as questionable heart disease patients but ultimately included in the no heart disease category. An additional 18 persons not examined a second time were classified by the cardiologists as having heart disease upon review of the findings of the first examination. A total of 131 persons classified as having diseases of the heart were thus found among the 386 examined persons. Of the 131 persons classified in the heart disease category, 99 fall in Group I above, 30 fall in Group II, and two cannot be included in either Group I or II. Persons who were found to have only one of the findings in Group II were not included in the heart disease group but were finally classified as having no heart disease. Thus, the no heart disease category includes twenty-four persons with systolic heart murmurs, 14 with only abnormalities of the electrocardiogram such as frequent ectopic ventricular and nodal contractions, carotid sinus sensitivity, etc., two with aortic aneurysm only, and twelve with only changes in the aorta: calcification, tortuosity, or dilatation.

The differential rates of sampling purposely employed and the failure experienced in successfully completing the examination of a large segment of the selected sample introduce complications in preparing the estimates of prevalence of the various diseases of the heart. The possible influences of the missing information will be examined later. However, a brief description of the methods of estimation employed which yield the rates in the following section is in order. If it is assumed that the group of cooperating persons from the sample in each stratum itself constitute a random sample of that stratum, the estimate of prevalence of diseases of the heart among the 7,130 persons 15 years of age or more would be prepared as follows: (1) estimate the number of cases of heart disease in each stratum by multiplying the calculated rate of heart disease among those persons examined from that stratum by the total number of persons in the stratum; (2) add the estimated cases for each stratum; and (3) divide the estimated total cases by 7,130. The estimates of prevalence for any subset of the strata, e.g., male rates or age specific rates, are calculated in the same way, ignoring the data from the other strata not included in the subset. The relevant information is included in columns (5) and (6) of the appendix table. Finally, since the 7,130 sample persons were selected from all the residents of the district with equal probability, the estimated rates of diseases of the heart in the total sample constitute unbiased estimates of the true prevalence rates for the entire district.

FINDINGS

All the findings will be presented in terms of prevalence of cases per 1,000 population.

From the estimated rates in Table I several interesting conclusions can be drawn. First, the over-all prevalence of heart disease among the age group of 15 years and above in the Arsenal Health District is estimated to be approximately 14 per cent. A second point to note is that, in total, the prevalence of heart disease among the females is almost half again that among the males. A large age differential in prevalence is apparent for both sexes.

The severity of heart disease may be characterized by the therapeutic classification[5] into which each case falls. The estimated distribution of the heart disease cases by therapeutic classification is shown in Table II.

TABLE I. ESTIMATED PREVALENCE OF HEART DISEASE BY AGE AND SEX
ARSENAL HEALTH DISTRICT, PITTSBURGH, 1953-1954

AGE	CASES PER 1,000 POPULATION		
	MALE	FEMALE	TOTAL
15-44	36	44	40
45 and over	231	342	289
Total	113 ± 33*	165 ± 39*	140 ± 24*

*This figure is twice the estimated sampling error.

TABLE II. ESTIMATES OF PREVALENCE RATES FOR HEART DISEASE AND PERCENTAGE OF CASES BY THERAPEUTIC CLASSIFICATION AND AGE
ARSENAL HEALTH DISTRICT, PITTSBURGH, 1953-1954

	THERAPEUTIC CLASSIFICATION*					
	A	B	C	D	E	TOTAL
Aged 15 to 44 years						
Cases per 1,000	3	14	23			40
Per cent	7	35	58			100
Aged 45 years and over						
Cases per 1,000	20	168	81	20	(less than 0.5)	289
Per cent	7	58	28	7	—	100
Aged 15 years and over						
Cases per 1,000	10	74	48	8	(less than 0.5)	140
Per cent	7	53	34	6	—	100

*"A": physical activity not restricted. "B": severe physical activity to be avoided. "C": moderate restriction of ordinary physical activity. "D": marked restriction of ordinary physical activity. "E": complete rest in bed or chair.

Table II shows that cases in therapeutic class A constitute only 7 per cent of all the heart disease cases, while the cases whose management requires some restriction of normal activity (B through E) constitute over 90 per cent of all cases. It may also be noted that cases requiring severe restriction of normal activity (D and E combined) constitute only slightly over 6 per cent of all cases. Two points concerning the age differences may be noticed. First, no persons in the age group 15 to 44 years were found to have heart disease of severity sufficient to warrant a therapeutic classification of D or E. In the older age group, however, 7 per cent of the heart disease cases are estimated to fall into the categories D and E. Second, the distribution of heart disease cases in the older age group is

concentrated in therapeutic class B (58 per cent) while the younger age group's distribution is concentrated in therapeutic class C.

Prevalence rates for the most frequently diagnosed types of heart disease are presented in Table III.

TABLE III. ESTIMATED PREVALENCE RATES FOR VARIOUS TYPES OF HEART DISEASE BY AGE AND SEX

ARSENAL HEALTH DISTRICT, PITTSBURGH, 1953-1954

AGE	SEX	TYPE OF HEART DISEASE CASES PER 1,000 PERSONS				
		RHEUMATIC	ARTERIOSCLEROTIC	ARTERIOSCLEROTIC AND HYPERTENSIVE	OTHER*	TOTAL
15 to 44	Male	29	—	2	5	36
	Female	39	—	—	5	44
	Total	34	—	1	5	40
45 and over	Male	1	72	64	94	231
	Female	7	91	195	49	342
	Total	4	82	133	70	289
15 and over	Male	18	28	27	40	113
	Female	26	37	79	23	165
	Total	22	33	54	31	140

*Includes hypertensive, toxic, and congenital heart disease, neurocirculatory asthenia, arteriosclerotic heart disease coexistent with anxiety state, and heart disease of undetermined origin.

DISCUSSION

From the brief methodologic description at the beginning of the paper it is apparent that the reported heart disease prevalence must be interpreted with caution. Two factors which influence the validity of the findings are (a) the diagnostic acumen of the physicians who examined the participants, and (b) the extent to which the nonparticipants differ from those persons who accepted the invitation to be examined.

Examining the nonparticipation factor first, the estimated rates are based on the assumption that participants and nonparticipants have similar heart disease characteristics. The validity of this type of assumption is always suspect. Furthermore, with only 54 per cent of the selected sample participating in the examination large differences in the two groups would seriously bias the estimates prepared from examination of participants only.

Two possible approaches to the nonparticipation problem exist. First, eliminate it (or at least markedly reduce the proportion of nonparticipants) by ascertaining the reasons for nonparticipation and designing investigations specifically to overcome them. Second, attempt to assess the possible nonparticipation influences on the estimated rates. From the present investigation we conclude that the time lag, 15 months, between the initial household survey and the beginning of the heart study was an important reason for the high proportion of the sample which was not examined. Many of the nonparticipants simply could

not be invited to attend the clinic as evidenced by the fact that only 518 of the 721 sample persons (72 per cent) were interviewed. Moving away from the district and deaths were the two principal reasons for noninterview. Lack of a cogent motivational appeal and a good method of communicating this motivation to the intended participants was also an important reason for the low participation rate. Finally, more attention should have been given to methods by which the examination might have been accomplished in the homes of the sample members for those persons not willing to attend the clinic. The nonparticipation rate can be reduced, but it requires advanced planning in full awareness of the consequences if this phase of the plan of investigation is not thoroughly considered.

The second approach to the nonparticipation problem, namely, attempting to assess the possible influence on the estimated rates of the failure to examine the total sample, is a difficult task. In the present instance, one or two interviews preceded the examination and many characteristics of the participants and nonparticipants could be compared. Some evidence of variation in the rate of participation by age, sex, and reported heart disease status was discernible. However, the sample was stratified by these characteristics so that this information does not necessarily imply bias in our results. Within each of the twelve strata the participants appear to be similar to the nonparticipants on the other characteristics examined, e.g., occupation, education, and economic and social status. A further comparison of the participants and nonparticipants who were interviewed during the study (518 persons) was planned and carried out. Prior to their examination, one of us (J. T.) made a tentative diagnosis from the extensive interview information for one half of those persons examined. The same procedure was carried out for the 132 persons who were interviewed but refused the examination. The proportion of tentative heart disease diagnoses in the two groups were in close agreement, and further the proportion of tentative diagnoses in the pre-examination group corresponded closely to the proportion of cases ultimately diagnosed after the examination.

Another partial check on the presence of bias in the estimated rates due to ignoring those persons who were not examined was undertaken. The prevalence of diseases of the heart was computed counting as cases, in addition to those diagnosed through physical examination, those among the 32 persons dying before examination who were reported to have heart disease by their family physician and those among the 132 persons who reported heart disease on interview but refused examination. For this latter group their own information given during the interview plus information from their family physician was utilized. The over-all rates of heart disease calculated from this combination of examination, interview, and family physician information remain essentially unchanged.

As a final attempt to assess the possible bias due to nonparticipation, the over-all prevalence rate was calculated by assuming that the nonexamined portion of the sample differed markedly from the rest of the sample. If the nonexamined group were to be examined and found to contain no persons with diseases of the heart the estimated prevalence of heart disease would be slightly in excess of 7 per cent. Since complete absence of heart disease in the nonexamined group is highly unlikely, we may safely assume that examination of all the sample persons would yield a rate greater than 7 per cent.

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The estimation of sampling errors for the rates included in this paper is, of course, also complicated by the nonparticipation problem. Some notion of the possible magnitude of these sampling errors may be obtained by calculating the variances under the same assumption as used in obtaining the rates—that the examined group in each stratum constitutes a random sample of that stratum. The sampling errors included in Table I have been thus calculated.

The problems of diagnosis in studies of this type also require additional study. As mentioned earlier the diagnoses were jointly made by a group of at least three of the cooperating cardiologists after a review of all the findings on each person. Undoubtedly, a number of persons have been placed in the category of no heart disease who could have been listed as questionable heart disease cases. It is likely, moreover, that among those persons classified as having heart disease there are some who would be considered as not having the disease by other clinicians. The design of the study did not include a scheme for measuring interphysician variation on diagnosis, and no internal assessment of possible "overdiagnosis" on the part of this group of cardiologists can be made. However, we believe that errors in diagnosing clinical heart disease where it does not exist are fewer than the errors of diagnosing no heart disease when, in fact, it does exist. The therapeutic classification of the diagnosed cases, Table II, sheds some light on the problem. With the definitions employed, the classifications A through E may be expected to overlap and shade into one another and not be clear-cut. Another group of cardiologists examining the same persons would perhaps not be able to duplicate the present findings. With respect to over-all prevalence estimates, however, we may assume that therapeutic class A contains the bulk of the incipient or minimal cases whose classification is likely to have the largest influence on over-all prevalence estimates. If these cases are removed from the category of heart disease and listed as doubtful, our over-all estimate is reduced from 14 to 13 per cent.

Despite the qualifications previously discussed that must be placed on the findings of this study, the results are interesting and raise a number of questions. Perhaps the most interesting finding is embodied in the over-all estimate of the crude prevalence rate of heart diseases in the population group surveyed, approximately 14 per cent. This rate is considerably higher than previously available information would have led us to expect. A frequently quoted figure based on the National Health Survey of 1936, with an adjustment for changes in the population since that date, places the national prevalence of the larger class of diseases, cardiovascular-renal disease, at 6 per cent.[1] Several factors must be considered, however, in any attempt to interpret the apparently high rate of prevalence obtained from our study.

Obvious factors that differentiate our estimate from that based on the 1936 National Health Survey are time (1936 vs. 1953-1954), the population group (National vs. Arsenal Health District), and the methods employed (interview survey of prevalence of diagnosed disease vs. examination survey by cardiologists). The net effect of these factors on the estimated rates is not known. However, we may point out that the age distribution of the persons residing in the Arsenal Health District is comparable to that for the whole of Pittsburgh and

Allegheny County, Pennsylvania, and except for a few characteristics the population of the Arsenal District resembles that of the rest of Pittsburgh. Therefore it would not seem reasonable to look for the explanation of the high rate in terms of peculiarities of the district itself. The possibility of bias in our estimate due to incompleteness of our examination data has been mentioned as another factor to consider. Finally, the diagnostic procedure and classification criteria employed in our study should be emphasized. Although the net effect of all the factors mentioned in this and the preceding section is unknown, it would appear that an estimate of 7 per cent as the crude rate of heart disease in the Arsenal Health District is on the conservative side.

Turning next to the distribution of cases by age and sex, our data indicate marked differences between the two sexes in prevalence of heart disease. If a finer subdivision of the age breakdown in Table I is employed we find the rates for men and women in the two age groups, 45 to 64 and 65 and older, to be, respectively, men 198, women 223; and men 216, women 766 per 1,000 population. This threefold increase in rate from the middle to the oldest age group among women is in sharp contrast to the almost constant rate in the corresponding age groups among the males. This information, although less reliable than that included in the preceding tables, furnishes interesting grounds for speculation. If the finding is accurate, do women survive their male counterparts once attacked by heart disease, or is the increased prevalence among the older women a result of a different age-incidence picture for the men and women? Our data, unfortunately, cannot answer these or other similar questions that could be raised.

In examining the rates in Table III, clinicians may be struck by the difference between the age-sex specific rates and the relative frequencies with which the various diagnoses have occurred, by age and sex, in their experience. For example, in the age group 15 to 44, none of our examined group had demonstrable arteriosclerotic heart disease, while the clinician on the basis of his experience might have the impression that such a diagnosis is not a rare occurrence in this age group. Other examples of similar discrepancy between clinical experience and our estimated rates occur in connection with the increased prevalence among the older women in contrast to the men mentioned above and in the sharp reduction in prevalence of rheumatic heart disease in the group over 45 years of age. With respect to the latter, it might be thought that the course of mitral stenosis, and particularly of aortic stenosis, would result in a higher rate of rheumatic heart disease in the older age group than that found. Comparisons of the relative frequency of a specific condition in a selected group, such as seen in most cardiac clinics and hospitals, with the corresponding rate in a cross section of a general population is always difficult. In the present instance we have calculated these rates because of their inherent interest, but their interpretation must include consideration of the precision of our estimates for particular age-sex classifications which, admittedly, cannot be considered high.

Finally, the 14 per cent heart disease prevalence estimate, if accurate, emphasizes the importance to be attached to these diseases both from an individual and a public health point of view. Before accepting this figure, however, the findings of this study should be verified by similar studies in other locations.

In designing such studies attention should be focused on overcoming the principal statistical weakness of the present study—the failure to examine 46 per cent of the sample. We believe that the nonexamination rate can be markedly reduced by learning the reasons for nonparticipation and designing investigations which remove or circumvent these obstacles to participation.

SUMMARY

This paper reports the methods and findings regarding prevalence of heart disease of a recently completed study conducted in the Arsenal Health District of Pittsburgh. The study involved a thorough physical examination of a random sample of the persons residing in the district by a team of cardiologists. The findings included an over-all estimate of 14 per cent for the prevalence of heart disease in the age group 15 years and over, 4 per cent prevalence in the age group 15 to 44 years, and 29 per cent prevalence in the age group of those over 45 years. Therapeutic classification and rates for rheumatic, arteriosclerotic, and hypertensive heart disease are also included. Problems arising due to nonparticipation of a large fraction of the selected sample are discussed.

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(*For Appendix see opposite page.*)

APPENDIX

Summary of Sampling and Estimation Procedure

STRATUM (INFORMATION FROM HOUSEHOLD SURVEY) (1)	NUMBER OF PERSONS IN STRATUM (2)	NUMBER OF PERSONS			ESTIMATED CASES IN STRATUM (6) = [(5) ÷ (4)] x (2)
		SELECTED FOR SAMPLE (3)	EXAMINED (4)	DIAGNOSED AS HEART CASES (5)	
A. Persons reported to have heart disease:					
Men					
Aged 15 to 44	20	20	15	7	9.3
Aged 45 and over	69	69	39	30	53.1
Women					
Aged 15 to 44	17	17	10	4	6.8
Aged 45 and over	87	87	36	27	65.2
B. Persons reported to have symptoms frequently associated with heart disease:					
Men					
Aged 15 to 44	72	37	24	4	12.0
Aged 45 and over	87	47	19	7	32.1
Women					
Aged 15 to 44	168	90	56	5	15.0
Aged 45 and over	236	154	77	34	104.2
C. Persons reported to have neither heart disease nor related symptoms					
Men					
Aged 15 to 44	1,975	54	38	1	52.0
Aged 45 and over	2,208	42	21	4	230.1
Women					
Aged 15 to 44	2,013	57	27	1	74.6
Aged 45 and over	1,178	47	24	7	343.6
Total	7,130	721	386	131	998.0

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Review

ACQUIRED IMMUNITY IN TUBERCULOSIS

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OCCURRENCE OF IMMUNITY TO TUBERCULOSIS

IN THE seventy-five years since Robert Koch first reported the isolation of the etiologic agent of tuberculosis,[1] much of the literature on this disease has been concerned with the problem of acquired resistance (immunity) to infection with *Mycobacterium tuberculosis*. The very existence of specific acquired resistance to tuberculosis has been questioned by many, and even in our own time some still maintain that immunity to tuberculosis does not occur.[2,3]

Informed opinion, however, now recognizes that tuberculosis does not constitute the single exception to the rule which states that recovery from an infectious disease will result in the acquisition of an increased resistance by the host to subsequent invasion by the etiologic agent. The evidence which leads inescapably to this conclusion has been given in the early reviews of Long,[4] Lange,[5] and Baldwin and Gardner,[6] and the more recent reviews of Fenner,[7] Rich,[8] Raffel,[9,10] and Rosenthal.[11] These reviews make it unnecessary to do more than summarize here the nature of the evidence which has proved that acquired resistance to tuberculosis does occur in both animals and man.

The evidence for the existence of acquired resistance to tuberculosis falls into three general categories: first, that evidence obtained from controlled experimental studies in laboratory animals; secondly, that obtained from observations on the course of the disease in man; and, finally, that furnished from controlled studies in which attempts have been made to protect human beings against tuberculous infection by vaccination with BCG (bacille Calmette Guérin) vaccine.

There can be no question that the exposure of several species of experimental animals, either to infection with small numbers of virulent tubercle bacilli, or to inoculation with immunizing agents such as avirulent tubercle bacilli, heat-killed tubercle bacilli, or chemically killed tubercle bacilli, and even fractions of the tubercle bacillus, will result in increased resistance to tuberculous infection. Such immunized animals, when sacrificed, show evidence of an increased tendency to localization of the subsequent challenge dose or evidence of a decrease in the extent of the disease as compared with the nonimmunized controls. Of equal importance is the fact that if the disease is allowed to take its natural course

the immunized animals have a markedly increased survival time as compared with nonvaccinated control animals. Finally, it can be shown that the multiplication of virulent tubercle bacilli actually is inhibited in the tissues of immunized animals.

Some of these phenomena will be dealt with at greater length in subsequent sections of this review, but taken together they leave no doubt that a substantial degree of acquired immunity can be induced in experimental animals either by infection or by vaccination with suitable agents.

The fact that tuberculosis is a chronic disease in which relapse is common has made it difficult to establish that acquired immunity plays an important role during the course of the disease in man. A perusal of the evidence as summarized by Rich[8] on this point, however, can leave no doubt in the mind of an unbiased observer that a controlled primary infection in human beings results in a substantially increased resistance to the disease. Furthermore, the actual resolution of the primary infection, whether in children or in adults, probably depends in large part upon the forces of acquired resistance which come into play some days or weeks subsequent to the initial infection as a result of the stimulation furnished by the infection itself. Certain experimental data which will have a bearing on this point will be brought out in the next section.

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Rich[8] has pointed out that the most convincing evidence for the occurrence of acquired specific resistance to tuberculosis in man would be the demonstration of the efficacy of a vaccination procedure for the protection of man against tuberculous disease. Numerous controlled experiments have been conducted on the immunization of human beings with BCG vaccine, and the results of these have recently been summarized by Rosenthal.[11] While the subject of vaccination of humans against tuberculosis will be dealt with in greater detail in the final section of this review, the evidence obtained from such studies indicates that a substantial amount of increased resistance to tuberculous infection can be furnished by vaccination with BCG. Although it is true that many of these studies contain defects which make a final evaluation of their validity difficult, the results of the well-conducted studies are such as to leave no doubt that vaccination with BCG affords an appreciable amount of immunity.

All the evidence, both experimental and clinical, points inescapably to the conclusion that both experimental animals and human beings may acquire an increased resistance to tuberculosis following either vaccination or exposure to the disease. What remains to be done with this knowledge is to elucidate the nature of this increased resistance so that the mechanism may be exploited to the greatest possible extent for the protection of man against tuberculous infection.

MECHANISMS OF IMMUNITY IN TUBERCULOSIS

In a recent review of the progress in our knowledge of tuberculosis, Dubos[12] came to the conclusion that few, if any, of the basic problems in the field had been resolved completely. One of the most important of these unresolved basic problems is the nature of acquired resistance to tuberculosis. While this point of view correctly denotes the state of affairs in so far as our knowledge of the final nature of the mechanism of immunity in tuberculosis is concerned, we now

do have available considerable information which permits us to define fairly precisely what happens when the immune mechanism is functioning. Moreover, the old controversy regarding the relationship of tuberculin allergy to immunity has been resolved.

At this point, it might be well to emphasize that there is little or no information available which provides a real clue as to the nature of virulence of mycobacteria. These organisms produce no exotoxins, no demonstrable endotoxins, no extracellular enzymes which might have a deleterious effect on the host, they form no capsular substance which protects them from phagocytosis, nor has any antigen been detected in virulent tubercle bacilli which can be correlated with virulence. The evidence for the participation of the "cord factor," recently described by Bloch and his associates,[13] in the virulence of mycobacteria is as yet unconvincing. Pathogenicity seems to be entirely a function of the ability of these microorganisms to maintain themselves and to multiply within the tissues of the host. Furthermore, these microorganisms are readily phagocytized and in vivo are found within macrophages in which habitat they are able to proliferate.

Role of Allergy.—The situation in regard to the nature of acquired immunity to tuberculosis has been greatly clarified by the demonstration by Rich and his colleagues[8] that guinea pigs immunized and also rendered hypersensitive by the injection of living tubercle bacilli could be desensitized by repeated injections of tuberculin without losing their acquired resistance to this disease. This furnished the first direct evidence that allergy and immunity in tuberculosis did not involve the same mechanism. Subsequently Raffel[14] found that the allergenic component of the tubercle bacillus consisted of a protein in combination with a wax. Injection of this protein wax complex would engender tuberculin hypersensitivity in guinea pigs, but guinea pigs made hypersensitive in this manner did not become immune to subsequent infection with virulent organisms.[15] Thus we have almost incontrovertable evidence that acquired immunity and allergy in tuberculosis comprise two distinct phenomena. This is not to say, however, that severe allergic inflammatory reactions occurring at the site of a tuberculous infection may not, at times, appreciably affect some of the defense mechanisms of the body including, possibly, those involved in acquired immunity.

Bacteriostasis and the Destruction of Tubercle Bacilli.—A variety of avirulent mycobacteria exist. Some of these are mutants of known virulent strains, and while they differ only slightly from the parent virulent strains in morphology, metabolic requirements, and antigenicity, they nevertheless are unable to produce progressive disease in animals. Useful information with respect to factors concerned with increased resistance to tuberculosis has been gained by comparing the fate of these avirulent mutants with the fate of virulent cultures in the tissues of immunized and nonimmunized experimental animals. For this purpose we shall cite data from one of the more recent more definitive studies which employed a technique which permitted the enumeration of the number of viable particles of tubercle bacilli in the organs of infected animals.[16] These experiments were carried out as follows: Cells of the avirulent H37Ra strain, a mutant of the virulent H37Rv strain of *M. tuberculosis* var. *hominis*, were injected intravenously into mice. At appropriate intervals following infection of approximately 40

million microorganisms 5 mice were sacrificed, and the lungs, livers, and spleens of each of these mice were homogenized mechanically. They were then diluted aseptically in a buffered solution containing albumin and small amounts of each dilution plated on an appropriate nutrient medium. Following incubation, the colonies of mycobacteria were counted, and the number of viable particles of mycobacteria in each of the organs was calculated. The results showed that these avirulent mycobacteria were rapidly destroyed in the liver from the very beginning, that the number of mycobacteria remained constant in the spleen for approximately 2 to 3 weeks following which they rapidly decreased in number, and that the numbers increased slightly in the lungs for approximately 2 to 3 weeks following which time the number rapidly decreased. This picture was the same regardless of the number of microorganisms injected.

When similar experiments were performed using various infecting doses intravenously of the virulent parent H37Rv organism,[17] the numbers of mycobacteria in the lungs increased rapidly, and the rate of increase was independent of the number of virulent organisms injected. Similar results were obtained when spleen and liver were cultured except that the rate of increase of the virulent mycobacteria in these organs was less rapid than in the lungs. Multiplication of the largest dose of virulent organisms administered continued until death of the animals occurred approximately 2 weeks after they were infected. However, multiplication of the smaller infecting doses of virulent organisms ceased after 2 to 3 weeks, and the number of organisms in each of the three organs remained constant for long periods thereafter.

These data indicate that nonimmunized mice initially can destroy avirulent tubercle bacilli in the liver, completely prevent multiplication in the spleen, and almost completely prevent multiplication in the lungs. However, between 2 and 3 weeks after intravenous inoculation with the avirulent tubercle bacilli, a change occurred in the mice, and they acquired the capacity to destroy the mycobacteria in the spleen and lungs, and to accelerate the destruction of these microorganisms in the liver. On the other hand, nonimmunized mice initially permitted the multiplication of virulent mycobacteria in all three organs, but again within 2 to 3 weeks, while all three organs of these mice acquired the capacity to inhibit the multiplication of small numbers, none of the organs showed any capacity to destroy the invading microorganisms.

From the standpoint of our interest in the nature of immunity to tuberculosis, the difference in the response at the end of 2 or 3 weeks in both immunized and nonimmunized animals is of particular interest. The most reasonable explanation for the acceleration of the destruction of the avirulent organisms on the one hand and the inhibition of multiplication of the virulent organisms on the other, is that at this period some immune mechanism acquired in response to the infecting dose begins to function.

This hypothesis was tested by conducting similar experiments using animals which previously had been immunized with BCG vaccine.[18] When the avirulent H37Ra strain was injected into animals previously immunized with BCG vaccine, the bactericidal process, which in the first experiment occurred only at the end of 2 to 3 weeks in the lung and spleen, was noted immediately in these organs,

and the rate of destruction in the liver was accelerated. Furthermore, in another experiment virulent H37Rv cells were injected into animals immunized with BCG vaccine. These results also confirmed the hypothesis since there was no evidence of any multiplication in any of the three organs of even the largest infecting dose. Nor did the animals acquire any capacity to destroy these virulent mycobacteria, since the number of viable particles of virulent mycobacteria which could be recovered from the organs remained constant for as long as 80 days.

From these data we conclude that the nonimmunized mouse can prevent the multiplication of avirulent mycobacteria in the spleen and perhaps in the lung but is unable to prevent the multiplication of virulent mycobacteria. The lungs and spleens of immunized mice, on the other hand, gain the capacity to destroy avirulent mycobacteria but only acquire the capacity to inhibit the multiplication of virulent mycobacteria.

Therefore, the immunized mouse responds to infection with virulent mycobacteria in a manner similar to the way in which the normal mouse responds to inoculation with avirulent mycobacteria.

A word of caution should be inserted here against the too ready acceptance of the hypothesis that a bacteriostatic mechanism is responsible for the static mycobacterial population of virulent microorganisms noted in the organs of immunized mice. The data merely show that a constant bacterial population is maintained in these organs; they do not differentiate between bacteriostasis, on the one hand, or a rate of bacterial multiplication which is just balanced by some bactericidal mechanism of the host, on the other. However, superficially at least, bacteriostasis provides a simpler and more probable explanation to the phenomenon. Therefore, in further discussion, it will be assumed that under such conditions the mechanism is one of bacteriostasis, even though proof for the operation of this mechanism is lacking.

Lurie[19] has conducted similar studies to determine the fate of virulent human and bovine type tubercle bacilli in the organs of rabbits. Although the refined techniques for the enumeration of the number of tubercle bacilli in the organs of animals used in the previous studies were not available at the time he conducted these experiments, his results show that multiplication of both types of virulent tubercle bacilli occurred initially in the organs of the rabbit. Within 2 to 4 weeks, however, multiplication of these organisms ceased, and actual destruction of the virulent organisms began to take place since the numbers of mycobacteria which could be isolated began to decrease. Destruction of the bovine type tubercle bacilli, organisms which are more virulent for the rabbit, was less complete than was the destruction of the human type bacilli. Also, destruction of all of the microorganisms in the organs of the rabbits did not occur, because as late as 6 months after injection the human type tubercle bacilli had not completely disappeared from the lungs and spleen. In a subsequent study in which he used rabbits which had recovered from inoculation with a small infecting dose of a human strain of the tubercle bacillus and therefore possessed some increased resistance, Lurie[20] noted that there was no evidence of multiplication of the reinjected human type tubercle bacilli and only slight evidence of multiplication of the bovine bacillus. Furthermore, destruction of the

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injected organisms took place more rapidly. The similarity between these results and those obtained with mice is apparent. Lurie[21] also has shown that rabbits which possessed an acquired resistance by virtue of previous infection, not only inhibited the multiplication of tubercle bacilli and brought about their destruction more rapidly, but also exhibited a capacity to mobilize more rapidly mononuclear phagocytes and had a tendency to more rapid formation of epithelioid cells and tubercles. Lurie[22,23] also feels that the more rapid mobilization of mononuclear phagocytes by the immune animal is an expression of increased physiologic activity conferred upon these cells by the tuberculous process, since not only did the mononuclear phagocytes accumulate more rapidly in response to the tubercle bacillus, but also to a nonspecific irritant such as mineral oil. Moreover, these mononuclear phagocytes exhibited increased phagocytic activity not only for tubercle bacilli, but also for unrelated particulate matter such as carbon or collodion particles. However, it is difficult to see how this increase in physiologic activity which is nonspecific could account for the specifically acquired ability of mononuclear phagocytes in immune animals either to inhibit the multiplication of mycobacteria or to destroy invading tubercle bacilli.

To summarize the experimental data: The immunized mouse appears to acquire the capacity to inhibit the multiplication of virulent mycobacteria, although it is quite possible that destruction of some of the virulent mycobacteria may take place at some period later than that observed during the course of these experiments; furthermore, the immunized mouse appears to respond to infection with virulent mycobacteria in a manner similar to the way in which the nonimmunized mouse responds to an inoculation with avirulent mycobacteria. In the rabbit, on the other hand, not only do immunized animals acquire the ability to inhibit multiplication of the invading microorganism, but apparently the mononuclear phagocytes of the rabbit also gain an increased capacity to destroy the invading tubercle bacilli. Also acquired resistance in the rabbit is characterized by a more rapid mobilization of mononuclear phagocytes and the more rapid formation of epithelioid cells and tubercles. The mouse, however, never shows any tendency toward the formation of epithelioid cells or the classical tubercles which are so characteristic a reaction to tuberculous infection in guinea pigs, rabbits, and men.[42]

Regardless of differences which may occur in the reaction of different species of animals to tuberculous infection there is apparently one outstanding feature in common in the reaction of immunized animals to infection, i.e., the development of the ability to inhibit the multiplication of tubercle bacilli. Although subsequent destruction of tubercle bacilli may or may not take place, depending upon the animal, a major manifestation of acquired resistance apparently is inhibition of multiplication of the invading microorganism. This fact has been commented upon also by other authors.[8,9]

There is much evidence to indicate that the course of events is similar in man, although quantitative data such as that given for mice and rabbits are not available. For example, primary tuberculosis in human beings bears all the earmarks of an infection which is characterized by rapid multiplication of the invading microorganisms followed by the development of an acquired immunity

which brings about inhibition of bacterial multiplication. Furthermore, it is well recognized that viable virulent mycobacteria may inhabit the tissues of man for prolonged periods, even years, a situation which is analogous, perhaps, to the animal experiments just discussed. Additional confirmatory data on this point will be found in the reviews of Rich[8] and Canetti.[25]

Role of Antibody.—While it is clear from the results of the experimental studies just given and from the course of the clinical disease in humans that immunity to tuberculous infection is characterized mainly by the acquisition of an increased ability to inhibit the multiplication of the invading mycobacteria, the mechanisms whereby the body brings about this bacteriostasis are still obscure. However, it is only natural first to investigate the possibility that specific antibodies, substances which are responsible for acquired immunity to the vast majority if not all of the other infectious diseases, might be responsible.

Antibodies are produced against a variety of protein and carbohydrate antigens found in the tubercle bacillus. These antibodies occur in the serum of patients suffering from the disease and in the serum of infected animals or animals which have been vaccinated with antigenic preparations. In experimental animals, however, no correlation can be found either between the presence of an antibody, or the amount of a given antibody, and increased resistance to tuberculous infection. Nor in patients has it been possible to show that recovery from the disease is associated with the appearance in the serum of a particular antibody. More information on this point can be obtained from Raffel.[9]

Proof of the existence of an antibody responsible for immunity to tuberculosis would consist of the demonstration that serum of an immunized animal did contain an absorbable substance with the characteristics of antibody, which when transferred to a nonimmunized animal would confer upon that animal an increased resistance to tuberculous infection. The numerous experiments of this type which have been conducted have been reviewed by Calmette,[26] Long,[4] Rich,[8] and Fenner.[7] The earlier experiments, none of which furnished convincing evidence that a protective substance was present in the serum of immunized animals, suffered from the defects that either too little serum was transferred, too few animals were employed, or serum from heterologous instead of homologous animals was used. Raffel[10] has recently reinvestigated this possibility in carefully controlled experiments using guinea pigs. Normal guinea pigs received for a period of 2 months daily 2.0 c.c. of serum subcutaneously which had been derived from the blood of immunized guinea pigs. Other guinea pigs were given similar amounts of normal serum and groups of guinea pigs also received 2.0 c.c. of whole blood derived from immune and normal donors. In addition, the control BCG-vaccinated animals were given normal serum to determine whether this serum would affect the immune state produced by vaccination. For the same reason another group of BCG-vaccinated animals received the same amount of whole blood from immune animals. The number of guinea pigs in each experimental group was 20 while each control group consisted of 15 or less animals. Following challenge with virulent organisms, the evaluation of the resistance of the animals to tuberculous infection was made on the basis of the relative amount of gross tuberculosis present in the viscera of the guinea pigs which were sacrificed and examined at an appropriate period following infection. No evidence of

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increased resistance to tuberculous infection was noted in any of the animals except in the controls which had been actively immunized with BCG vaccine.

The results of this beautifully controlled experiment might be taken as conclusive evidence that antibody plays no role in acquired immunity to tuberculosis in guinea pigs if it were not for the fact that, in the first place, guinea pigs are notoriously poor antibody formers and, secondly, that the evaluation method employed, i.e., the estimation of the amount of gross visceral tuberculosis in infected animals after a certain arbitrary length of time, is very insensitive. Small increases in resistance which might have occurred by virtue of some substance transferred in the serum might not have been detected by such a gross evaluation method.

Recently Seibert[27] has suggested that the simultaneous presence of antibodies to tuberculoprotein and tuberculopolysaccharide, as well as complement-fixing antibodies, may be necessary before immunity to tuberculosis can exist. However, no passive transfer experiments to test the protective effect of antisera containing these antibodies were conducted.

Other attempts to demonstrate the involvement of antibody in acquired immunity to tuberculosis have included experiments in which the capacity of blood from immune animals to inhibit the multiplication of tubercle bacilli has been tested both in vitro and in vivo. While the evidence is somewhat contradictory, there is no real indication that the serum of immune animals acquires any appreciable capacity to inhibit the multiplication of tubercle bacilli in vitro.[28] Experiments of this nature are complicated by two factors: first that normal serum itself may exert an inhibitory effect in concentrations over 10 per cent, and, secondly, by the difficulties which are encountered when attempts are made to measure accurately the rate of multiplication of tubercle bacilli in vitro.[29] It would be worth while repeating such tests using a method now available which makes possible the accurate measurement of the rate of growth of very small numbers of tubercle bacilli.[30]

The presence of possible humoral inhibitory factors also has been tested by making observations on the multiplication of tubercle bacilli in vivo. Lurie[31] approached this problem by injecting virulent tubercle bacilli incorporated in 6.0 per cent sterile agar subcutaneously into rabbits. At appropriate intervals these agar islands were examined by bacteriologic and histologic methods. His results showed that there was a pronounced inhibition of multiplication of the tubercle bacilli in the agar blocks in immunized animals as compared with non-immunized controls. Lurie subsequently obtained similar results[32] in a study in which tubercle bacilli were placed in collodion sacs instead of agar and the sacs then placed in the peritoneal cavity of normal and immunized rabbits and guinea pigs. The conclusion that Lurie derived from these experiments was that since the tubercle bacilli were protected within the agar or collodion sacs from phagocytic cells, there was some humoral factor, possibly antibody, which exerted a deleterious effect upon the mycobacteria. Woodruff[33] also found that the free growth of human type tubercle bacilli on, or within the cells, of the omentum of the guinea pig did not occur in immunized animals.

Raffel,[10] on the other hand, was unable to confirm the findings of Lurie using a somewhat different technique. He employed plastic capsules one end of which

supported a gradocol membrane. Measured numbers of tubercle bacilli were placed in these capsules which were then implanted in the peritoneal cavities of normal and immunized guinea pigs. At intervals up to 3 months the capsules were removed from the animals of both kinds and the number of tubercle bacilli in each measured quantitatively by plating. No evidence was obtained that the growth of tubercle bacilli was inhibited in the peritoneal cavities of immunized guinea pigs to a greater extent than in the normal.

The promotion of phagocytosis, one of the major mechanisms whereby antibody accounts for acquired immunity in many other infectious diseases, apparently plays little if any role in acquired resistance to tuberculosis, since tubercle bacilli are phagocytized very rapidly by the neutrophils and macrophages of nonimmunized animals. However, there is some evidence that antibody against tubercle bacilli may stimulate phagocytosis slightly.[34,35] The work of Lurie[23,36] would suggest that antibody is not concerned with the destruction of tubercle bacilli within the monocytes.

From the foregoing review it is apparent that the evidence which might implicate specific antibody as the agent responsible for acquired immunity to tuberculosis is very scant. The only really positive evidence to this effect is the aforementioned work of Lurie in which there apparently was an increased inhibition of multiplication of tubercle bacilli implanted in immune animals as compared to nonimmunized control animals. This phenomenon, however, as pointed out by Dubos,[37] might be accounted for by the accumulation of toxic inhibitory organic acids about the more intense inflammatory focus which would occur in the immune and also hypersensitive animals.

Further evidence, although indirect, contributory to the possible role of antibody in immunity to tuberculosis can be gained by a study of the reaction to tuberculous infection of individuals who have a decreased capacity to produce gamma globulin. Such agammaglobulinemic individuals are notoriously more susceptible to those infectious diseases where it is known that acquired resistance depends upon the operation of specific antibody.[38] It has been reported,[38,39] however, that in the few such individuals who have had tuberculosis, the course of the infection was not accelerated over that seen in nonagammaglobulinemic individuals and, under appropriate therapy, recovery took place in the normal manner.

A high degree of specificity is one of the outstanding features of all antibody mediated reactions, including immunity. Therefore, information on the role of antibody in immunity to tuberculosis also may be obtained by an examination of the specificity of acquired resistance to this disease, even though the usefulness of evidence of this kind will involve the acceptance of the not necessarily valid premise that any immune mechanism which did not involve antibody would be nonspecific. To my knowledge, there is no evidence which would suggest that people who have tuberculosis are more resistant to other infectious diseases. On the other hand, the intriguing hypothesis might be proposed that the failure of the majority of people to develop clinical tuberculosis after becoming infected with tubercle bacilli for the first time possibly might result, in part at least, from the operation of immune forces acquired from previous exposure to some other

microorganism. Experimentally, the evidence on this point is scant. Nyka[40] has shown that animals immunized with *Brucella abortus* have an appreciably increased resistance to experimental tuberculous infection. Dubos and Schaedler[41] found that mice immunized with *Hemophilus pertussis* also were more resistant to tuberculosis. Swedberg[42] and Youmans and Youmans,[43] on the other hand, have failed to show that *Hemophilus pertussis* vaccine increased the resistance of mice to infection with *Mycobacterium tuberculosis*. More work is needed on this interesting point.

The recent finding by Youmans, Millman, and Youmans[44] that certain small intracellular enzymatically active particles, which in many of their characteristics resemble mitochondria, are potent immunizing agents against tuberculous infection in mice also might be used as evidence against antibody as the agent responsible for immunity in tuberculosis, since in other infectious diseases the antibody responsible for acquired immunity is directed toward either a capsular antigen or an antigen found in or upon the surface of the bacterial cell.

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In spite of the negative evidence, I am reluctant to discard completely the hypothesis that some kind of antibody is involved in acquired immunity to tuberculosis since it would be the only microbial disease, with the possible exception of anthrax, in which a specific antibody did not play an important part in the immune process. As Rich[8] has so aptly stated, "Nature may be prodigal of materials, but she is rigorously economical of method."

It may be that the technical methods presently available are inadequate to detect the small amounts of the particular antibody involved. It is only in recent years that we have become aware that antibodies may vary considerably in composition and reactivity.[9,45] The antibody responsible for tuberculous immunity may occur in some other serum globulin fraction than gamma globulin, thus explaining the resistance of agammaglobulinemic individuals to tuberculosis. The failure to demonstrate passive transfer of immunity with the serum of immunized animals may be because the antibody is located primarily within phagocytic cells, perhaps the macrophage, rather than in the blood serum. In this connection it is worth while recalling that the antibody responsible for tuberculin allergy was first detected within leukocytes[46] obtained from the peritoneal cavity of tuberculin-sensitive guinea pigs, although recently it has been found also in small amounts in serum.[47] Finally, since the major manifestation of acquired immunity to tuberculosis is the inhibition of multiplication of tubercle bacilli, the antibody may be located not only intracellularly, but be of the "ablastic" type. "Ablastin" is an antibody-like substance which has been found to have the property of inhibiting the multiplication of *Trypanosoma lewisi*.[48] Too little is known about the reproductive mechanisms of the tubercle bacillus to assume that it could not be inhibited in some such manner. This possibility also has been brought out by Rich.[8] In support of the operation in immunity to tuberculosis of some as yet undetected antibody is the fact that the time of appearance and the persistence in the animal of this immunity follows the pattern made familiar by those diseases in which antibody is the responsible agent. Furthermore, it can be demonstrated experimentally that immunity to tuberculosis increases more rapidly following a second injection of the immunizing substance than following the initial immuniz-

ing injection.[43] In other words, the familiar anamnestic reaction so characteristic of antibody formation can be demonstrated.

Role of Phagocytic Cells.—In the absence of any directly demonstrable indication that antibody is involved in acquired resistance to tuberculosis, many investigators have turned their attention to the role of the phagocytic cells in this process, hoping to find in some altered characteristic of these cells the answer to the problem. Tubercle bacilli are rapidly phagocytized in vivo by both neutrophils and macrophages shortly after they enter the body and become more or less permanent residents within macrophages. In this habitat the tubercle bacilli metabolize and multiply and eventually may destroy the host cell which then disintegrates, setting the tubercle bacilli free, whereupon the microorganisms are rephagocytized by other macrophages. This process may occur repeatedly and, unless controlled, will result eventually in tissue destruction and clinical tuberculous disease. However, with the appearance of acquired immunity, multiplication of the microorganisms apparently ceases, and they appear to be able to remain viable, but nonmultiplying, within the macrophage for extended periods. This naturally focuses attention upon the macrophage as the agent primarily responsible for acquired immunity to tuberculosis and suggests the possibility that the acquired immune process may involve, in some unknown way, the alteration or adaptation of the macrophage so that it can cope more successfully with the contained bacteria. This view is favored by Raffel.[10] Lurie[36] has tested this hypothesis by permitting monocytes obtained from both normal and tuberculous rabbits to phagocytize virulent tubercle bacilli in vitro in the presence of serum from both normal and immunized animals. These mixtures were then inoculated into the anterior chamber of the eye of normal rabbits. The proliferation of the tubercle bacilli contained therein was studied both by plate counts and from microscopic sections of the involved tissue. He reported that there were far fewer bacterial cells present in the anterior chambers of the eyes that received the mixtures containing the tubercle bacilli and monocytes from immune animals regardless of whether serum from normal or immunized animals was used. Rich[8] has criticized these studies because a human variety of *Mycobacterium tuberculosis* was used, an organism to which the rabbit is normally very resistant, and, secondly, because of the lack of reliability of the plate-counting technique. Mackaness[49] has pointed out that in transferring cells from a tuberculous animal, hypersensitivity also is transferred, and the subsequent allergic reaction might have been involved in the inhibition of the multiplication of the tubercle bacilli. Lurie,[50] however, disputes this interpretation and feels that the most reasonable explanation is that the cells of the immune host retain an increased capacity to inhibit multiplication of tubercle bacilli. Raffel[10] has studied this problem using a similar technique except that capsules containing the monocytes and the bacilli were implanted intraperitoneally into normal guinea pigs. He reported that there was no indication that there were fewer tubercle bacilli present in the capsules containing monocytes obtained from immunized animals than in those capsules containing monocytes from normal animals.

This problem also has been approached using monocytes cultivated in tissue culture. Suter[51,52] reported that in tissue cultures monocytes obtained from the

peritoneal cavity of guinea pigs immunized with BCG had a greater capacity to inhibit the multiplication of tubercle bacilli than did macrophages obtained from the peritoneal cavities of normal guinea pigs. Mackaness,[49] on the other hand, has reported that in tissue cultures those monocytes obtained from vaccinated rabbits had no greater capacity to inhibit the growth of virulent tubercle bacilli than did monocytes from normal animals. Raffel[10] feels that these and his own confusingly contradictory results can probably be explained on the basis of the lack of some essential technical refinement. This point of view is supported by the work of Fong, Schneider, and Elberg[53] who have shown that the viability of the monocytes in the tissue cultures is of prime importance and that the role of cells in immunity to tuberculosis can be assessed only under carefully controlled conditions. Using a refined technique which maintained constant numbers of monocytes for the experimental period, these authors investigated the effect of tubercle bacilli on the viability of monocytes in tissue cultures. They found that there was less degeneration of the monocytes when they were derived from immune animals and were exposed to virulent tubercle bacilli in the presence of immune serum. These monocytes were more susceptible when exposed to virulent tubercle bacilli in the presence of normal serum. Monocytes derived from normal animals also were more susceptible than monocytes from immune animals when exposed to virulent tubercle bacilli in the presence of both normal and immune serum. The implication from this study is that not only may an alteration occur in the macrophage of the immune animal, but a substance found in serum also may be essential in acquired immunity. It should be emphasized, however, that this work was essentially a study of the survival of macrophages in tissue culture and not a study of the survival of tubercle bacilli.

The evidence for the acquisition of an increased capacity by the macrophages of immunized animals to inhibit the growth of virulent mycobacteria is not entirely negative, but the evidence is so contradictory that we cannot, at the present time, assume that an acquired cellular immunity to tuberculosis does exist.

Other Mechanisms.—Other mechanisms which might account for the acquired immunity to tuberculosis have been investigated. Dubos, for example,[54-56] has suggested that organic acids, particularly lactic acid, which tend to accumulate in areas of inflammation may exert an inhibitory action upon the tubercle bacilli. Raffel,[9] however, has pointed out that should this mechanism play an important role in acquired immunity to tuberculosis, then the allergic reaction also should play an important role in increased resistance to this disease. This is apparently not the case. The possibility has been investigated by Raffel[10] that macrophages of immunized animals may develop an ability to utilize atmospheric oxygen at a faster than normal rate, thus depriving the bacilli within their cytoplasm of this element to a degree incompatible with continued assimulation and proliferation by the microbes. Since *Mycobacterium tuberculosis* is a strict aerobe, a lowering of the oxygen tension might reduce the rate of multiplication. While Raffel has reported an increased oxygen uptake by macrophages of immune guinea pigs over that of normal animals, the significance of this finding has yet to be determined.

In addition to the studies mentioned earlier in which attempts were made to detect in serum of immunized animals some substance which would have an

inhibitory effect on the growth of tubercle bacilli, experiments have also been conducted to determine the bacteriostatic activity of a variety of tissue extracts from the organs of animals.[57-61] There is, however, no convincing evidence which would indicate that extracts of the tissues of immunized animals have any greater capacity to inhibit the growth of tubercle bacilli than do similar preparations made from the tissues of nonimmunized animals.

Myrvik and Weiser[62] have shown that virulent tubercle bacilli are quite susceptible to the action of lysozyme. These authors have also demonstrated that the lysozyme content of the serum of rabbits is increased following vaccination with BCG. Extensive experiments conducted by Youmans and Youmans in collaboration with Weiser and Myrvik have failed to show, however, that the course of an experimental tuberculous infection in mice produced with human type tubercle bacilli could be significantly affected by the administration to the mice of high concentrations of crystalline egg white lysozyme.

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THE PRODUCTION OF IMMUNITY IN EXPERIMENTAL ANIMALS

Measurement of the Immune Response.—Factors which have been responsible, largely, for the lack of development of our understanding of fundamental mechanisms in the host-parasite relationship in tuberculosis, are, on the one hand, the absence of methods which would permit accurate measurement of many of the phenomena which have been investigated, and, on the other, the failure of many investigators to use an accurate method even when one is available.

Proper measurement involves not only the use of sensitive, reliable, and valid methods, but just as importantly should involve, when necessary, the use of analytical statistical procedures which permit the proper evaluation of the significance of data.

The nature of the mechanisms involved in acquired resistance to tuberculosis and the problems involved in the development of a potent, nonviable vaccine against tuberculous infection can be solved only by the experimental use of laboratory animals under properly controlled conditions and by the application of suitable evaluation procedures.

In the study of the phenomenon of immunity, laboratory animals usually are vaccinated with either living mycobacteria or some fraction thereof, and at some subsequent time these animals are challenged with an infecting dose of a virulent mycobacterium. Measurement of the amount of increased resistance in the vaccinated animals then is attempted using usually one of the three following procedures.

First, at some arbitrarily selected time following challenge, both vaccinated and control animals are killed, and a visual estimate is made of the relative amount of gross and microscopic disease found in the organs and tissues of the animals of the two groups.[63,64] That this is a highly subjective and therefore very inaccurate measurement of the amount of disease in the animals should be evident. Using such a procedure, it is impossible to determine with any precision the actual amount of immunity produced.

The second method of evaluation involves the calculation of the mean or median survival times of both vaccinated and control animals following challenge

with virulent tubercle bacilli.[42,43,65-69] This can be a reliable and accurate measurement of the response of animals to tuberculous infection and can be used for the quantitation of the degree of immunity providing the deaths of both vaccinated and control animals are normally distributed.[42,43] I have shown in a recent publication, however, that the distribution of deaths of vaccinated mice following challenge with virulent human type tubercle bacilli may not be normal, whereas the distribution of the deaths of the control animals may be normal.[43] In such a situation neither the mean nor the median survival times can be used as valid measures of the average response, instead, the number of animals which survive longer than a certain standard time period should be recorded and compared.[43]

Finally, there have been a number of studies in which the response of immunized mice to infection with *Mycobacterium tuberculosis* has been followed by actually counting and comparing the number of tubercle bacilli found in the organs of the infected normal and immunized animals.[67,68,70] This has been done by the employment of the mycobacterial enumeration technique described earlier in this article. Such a procedure, while it does give information on the actual numbers of tubercle bacilli in the infected normal and immune animals, is extremely laborious and technically difficult. Also, as will be brought out later, because of the large variation in the numbers of tubercle bacilli in the organs of different animals, the use of too few animals easily may lead to erroneous conclusions. Finally, the finding[18] that little or no change in the numbers of virulent tubercle bacilli may take place in the organs of immunized mice for long periods casts doubt on the validity of this method for measurement of the amount of acquired resistance in experimental animals.

Immunogenicity of Intact Mycobacterial Cells.—Because of the importance to man of the preparation of a specific vaccine for the prevention of tuberculosis, the experimental production of immunity in animals has occupied the attention of a large number of investigators from the very beginning. A variety of potential immunogenic agents have been tested including living virulent, living avirulent, and living saprophytic tubercle bacilli; tubercle bacilli killed by chemical or physical means; and a wide variety of extractives of tubercle bacilli. It is unnecessary here to cover the details of the early studies since they have been adequately described by Calmette,[26] Long,[8] Swedberg,[42] Fenner,[7] Raffel,[10] and Rosenthal.[11] Furthermore, because of technical inadequacies as outlined above, the majority of the older studies do not provide information on the actual amount of immunity produced, a deficiency which has been pointed out also by Schwabacher and Wilson.[66] The general conclusion can be drawn from these early studies, however, that the most effective immunizing agents are those composed of living virulent or avirulent mycobacteria, and more recently this conclusion has been confirmed by experiments which have employed more sensitive and more quantitative methods.[42,43] For example, it can now be shown that the immunization of mice with heat-killed tubercle bacilli will result in the production of an amount of immunity which is only about one-half that produced by an equivalent number of living microorganisms. On the other hand, tubercle bacilli killed by ultraviolet irradiation may lose nearly all capacity to produce immunity in mice.[43]

No completely adequate explanation has been offered for the greater immunogenicity possessed by living tubercle bacilli, though several possible explanations have been proposed, as follows:

First, the method of killing may destroy or alter some relatively labile immunogenic complex. This explanation is supported by the lability of the highly immunogenic particles recently isolated from mycobacteria by Youmans, Millman, and Youmans.[44]

Second, since even avirulent tubercle bacilli may remain viable for many days following introduction into the tissues, these living tubercle bacilli may elaborate an immunizing substance which is not ordinarily produced when these microorganisms grow in vitro. This would be closely analogous to the anthrax situation.[71]

Third, the microorganisms while metabolizing in vivo may produce additional amounts of an immunogenic substance also possibly produced in vitro.

Fourth, the number of tubercle bacilli initially injected may be too small to produce a pronounced immunogenic stimulus but, during a period of multiplication following introduction into the tissues, may, because of the increase in numbers, thereby increase the amount of immunogenic substance to the point where an appreciable immune response will result. This mechanism differs from the third mechanism just mentioned only in the respect that actual multiplication of the tubercle bacilli in vivo is involved, and, therefore, the increase in the amount of immunogenic substance would be primarily a function of the increase in number of tubercle bacilli, rather than the result of the production of more substance by a fixed number of cells.

Role of Bacterial Multiplication in the Production of Immunity.—The popular concept[7,37,72] that mycobacterial multiplication may play an important role in the development of acquired immunity when small doses of a vaccine composed of living cells is used demands careful examination. The most familiar mycobacterial vaccine is composed of living cells of the BCG strain of *Mycobacterium tuberculosis* var. *bovis*. This culture, while it does not produce progressive disease in animals or human beings, has always been regarded as partially virulent because of its ability to produce self-limited lesions when inoculated intradermally into guinea pigs and man,[11,73] and also because the injection of very large doses subcutaneously may result in local abscess formation and enlargement of the regional lymph nodes in guinea pigs.[74] Such findings, however, may represent the allergenic potency of a culture rather than bacterial multiplication. Lurie, however, using a bacterial enumeration technique, has reported that BCG will multiply in the organs of rabbits following intravenous inoculation.[75] However, for his microbial determinations this investigator sacrificed only two animals at each time interval, and the small increases which he noted in some of the organs within the first two weeks could easily have been more apparent than real and could have resulted from the enormous variation which is known to occur between the bacterial content of the organs of different animals. Actually, the coefficient of variation can be as high as 75 per cent in such experiments.[17] On the other hand, the large and therefore possibly real increases which Lurie noted in the bacterial content of tracheobronchial and mesenteric lymph nodes might have represented the accumulation of mycobacteria draining from adjacent

tissues and organs rather than actual multiplication. Dubos and his associates,[72,76-80] in a series of publications, have investigated the characteristics of several mycobacterial strains, including several substrains of BCG, and have followed the fate of these cultures in the organs of mice using the plate-counting technique described earlier in this review. On the basis of their results, Dubos and associates have suggested that mycobacteria be divided into three categories: virulent, those capable of multiplying in vivo and producing progressive disease and death; attenuated, those capable of multiplying for only a limited period in vivo; and avirulent, those mycobacteria which have no ability to multiply in vivo. In addition, these investigators reported that the immunizing potency of substrains of BCG was directly related to their capacity to multiply and maintain themselves in the organs of mice. Finally, progressive fatal disease could be produced with BCG in mice whose resistance to infection had been lowered by a nutritionally deficient diet or the administration of thyroid extract. The data presented by Dubos and his associates, however, are scant and much of it shows such variation between individual microbial determinations as to raise some doubt about the actual occurrence of multiplication of the attenuated strains of mycobacteria. This question recently has been re-examined by Sever and Youmans.[17] Two strains of mice were used, the "Strong A" and "C57," and the following three strains of mycobacteria: a potent immunizing strain of BCG, the R1Rv attenuated strain, and the avirulent H37Ra strain. These experiments were conducted with meticulous attention to the many sources of technical error, and the large variation between the number of mycobacteria found in the organs of five mice was calculated each time the animals were sacrificed. When the mean number of mycobacteria of both BCG and the R1Rv strains was calculated for each time interval and the large variation in numbers of mycobacteria which occurred between different mice was taken into account, it was found that the course of events did not differ significantly from that which occurred when the avirulent H37Ra strain was injected into mice. Neither the BCG strain nor the R1Rv strain multiplied to any appreciable degree in any of the three organs examined (lung, liver, spleen) of either strain of mouse, except for an early slight transient increase in numbers in the lungs which also occurred in mice injected with the H37Ra strain.

The results were the same regardless of whether very small or large numbers of tubercle bacilli were injected into the mice. These careful studies cast considerable doubt on the validity of the concept that so-called attenuated strains of mycobacteria have any greater capacity to multiply in the organs of mice than do avirulent strains. Since small numbers of organisms of the BCG strain employed in this study also produced a high degree of immunity in the same strains of mice in which little or no multiplication of the microorganisms was observed, no relationship can be claimed between ability to multiply in vivo and capacity to immunize. Of course, similar precise measurements must be made using other animals before the assumption can be made that BCG and similar organisms do not multiply in the organs of other animals. Actually, however, Kanai and Yanagisawa,[81] and Kanai, Katsuyama, and Yanagisawa[82] have reported that a strain of BCG did not multiply either in the lung, liver, or spleen of guinea pigs, whereas the H37Ra strain did increase in numbers in the spleen.

How can we account, however, for the substantial degree of immunity known to be produced with the small vaccinating doses employed intradermally in human beings if cultures such as BCG do not multiply following inoculation? There are several possible explanations. First, it is evident that the dose inoculated does furnish a potent antigenic stimulus because the majority of people vaccinated with BCG acquire an appreciable degree of tuberculin hypersensitivity. It is quite possible that protective antibody, or protective substance, might be formed to the same degree. Secondly, it has been shown by Freund and co-workers[83] that tubercle bacilli have an adjuvant effect on the production of antibody to other antigens, therefore, such an adjuvant action on the production of antibody to the antigens of the tubercle bacillus itself could occur. Also, it is well known that many substances are more apt to be antigenic when introduced by way of the skin.[84,85] Finally, even though the introduction of such a small amount of vaccine intradermally did not result per se in the production of a high degree of immunity it might very easily condition the body so that it would react anamnestically by a much more rapid production of protective antibody, or protective substance, in response to a stimulus furnished by the virulent tubercle bacilli at the time the individual becomes infected.[43] The slow growth of virulent tubercle bacilli in the host might permit the anamnestic production of a high degree of immunity before the infection had time to become clinically evident.

There has been a great tendency to associate immunizing potency with virulence and therefore to assume that the more an immunizing strain such as BCG resembled virulent strains, without actually producing disease, the better an immunizing agent it would be.[7,11,72] Although, because of the conflicting nature of the evidence given above no final conclusion can be drawn at this time, I feel that this concept needs critical re-evaluation. The immunizing potency of any given strain of living mycobacteria could easily depend, for the reasons enumerated above, solely upon the amount of immunogenic substance present in the injected cells, or possibly upon the amount elaborated in vivo by metabolizing, but nonmultiplying, microorganisms.

Immunogenicity of Fractions of the Tubercle Bacillus.—In spite of the fact that living microorganisms have been found to be the most effective immunizing agents against tuberculous infection, numerous attempts have been made to isolate and identify the immunizing substance. From the practical standpoint there is the hope that, could such a substance be isolated and identified, it might be administered to humans in greater amounts, with greater safety, and with the elimination of the complications introduced by the allergenic propensities of living mycobacterial cells. Many of the unrewarding early attempts in this direction have been included in the references given at the beginning of this section. In recent years, however, Choucron[86,87] has claimed that a mineral oil extract of tubercle bacilli permitted the isolation of a lipopolysaccharide which would produce a high degree of immunity to tuberculous infection in guinea pigs, and Kropp and Koley[88] and Kropp and Floyd[89] have reported the isolation of a carbohydrate-lipid complex which possessed immunizing properties. However, these studies lack adequate confirmation. Recently, Weiss and Dubos,[90,91] and Dubos, Weiss, and Schaedler[92] have reported that the "Antigen Méthylique," of Boquet and Nègre[93] would produce a substantial degree of immunity in mice.

This substance is essentially a methyl alcohol extractive of killed tubercle bacilli and, according to Nègre,[94] will only produce transient increases in the resistance of guinea pigs to tuberculous infection. In my own laboratory, all attempts to produce a significant degree of immunity in mice with methyl alcohol extracts of tubercle bacilli have been failures.[95]

More recently, Youmans, Millman, and Youmans[44] have reported that a highly immunogenic substance could be separated from avirulent mycobacteria by mechanical means. These authors ground large masses of tubercle bacilli in a ball mill with powdered glass in a phosphate buffer isotonic sucrose solution. Following grinding at 4° C. for several hours, the unbroken whole cells and debris were centrifuged out at low speed. The supernatant was then centrifuged several times at increasing speeds in an ultracentrifuge and all sediments discarded except the final one which was obtained after 3 hours of centrifugation at 40,000 RPM (144,700 × G). This final sediment was resuspended in isotonic sucrose buffer solution and upon examination under the electron microscope was found to be composed of very small particles which varied in diameter from about 20 mμ to 100 mμ. These particles were electron dense and were enzymatically very active. Upon injection into mice they were found to produce just as high a degree of immunity as that obtained following the injection of large numbers of the whole living cells of the same mycobacterial culture from which the particles had been prepared.

The particles were easily disrupted by electron bombardment, and the immunogenic potency was decreased by exposure to sonic vibration, by lyophilization, and by heat. Preliminary results indicate that these particles apparently do not sensitize guinea pigs to tuberculin. It is too early to assess the practical significance of these findings.

VACCINATION OF MAN AGAINST TUBERCULOSIS

The history of the vaccination of human beings against tuberculosis is mainly the history of BCG vaccine (bacille Calmette Guérin). This vaccine is composed of living cells of a strain of *Mycobacterium tuberculosis* var. *bovis* which was attenuated by growth and repeated subculture on a bile-potato medium.[96,97]

A variety of other vaccine preparations have been employed, or have enjoyed temporary popularity, including tubercle bacilli killed by various means, acid-fast organisms isolated from cold-blooded animals, and attenuated human type tubercle bacilli. The origin and use of these has recently been reviewed in detail by Rosenthal.[11] More recently in Great Britain, considerable attention has been paid to the immunizing potentialities of the vole bacillus, (*Mycobacterium muris*), a mycobacterium isolated from a field mouse, the vole.[98,99] This organism will not produce disease in man but will stimulate the production of immunity against both bovine and human type tubercle bacilli in experimental animals. Recently in man it has been shown also to be an effective immunizing agent.[100] It seems to produce, however, a greater proportion of untoward reactions in human beings than does BCG vaccine.

The vast majority of vaccinations in man, however, have been performed with BCG. Since the first announcement of the vaccination of human beings

with this organism in 1924,[101] well over a hundred million people have been inoculated with this vaccine.[11]

The history, effectiveness, characteristics, safety, preparation, preservation, methods of administration, and the comparison of the effectiveness of BCG with other vaccines has recently been brought up to date in a book by Rosenthal.[11] Readers wishing detailed information on any aspects of BCG vaccination should consult this excellent treatise. An earlier short review on BCG is provided by the publication of Fenner.[7]

Although an effective vaccine would be of material aid in the control of tuberculosis, BCG vaccine has not been universally employed. In the United States, objections to the use of BCG vaccine have, for the most part, centered around the following points: (1) *Efficacy:* The feeling on the part of many that there was no convincing evidence that BCG vaccine actually would produce a significant degree of acquired immunity to tuberculosis in man. (2) *Safety:* The fear on the part of many physicians that since this vaccine is composed of living organisms, the organisms might regain their virulence and produce infections in human beings. (3) *Allergenicity:* Since vaccination with BCG will induce in the vaccinated subject an appreciable degree of tuberculin allergy, not only would the diagnostic usefulness of the tuberculin test be destroyed, but the vaccination of tuberculin-positive individuals becomes difficult. These points will be considered individually.

The Efficacy of BCG Vaccine for the Prevention of Tuberculosis in Man.— Before examining the specific evidence relating to the effectivness of BCG vaccine for the prevention of tuberculosis in man, it might be well to consider briefly what actually can be expected from the vaccination of human beings against a disease such as tuberculosis. The experimental evidence given in the earlier part of this review, which, as has been pointed out, can be correlated with the course of events in tuberculous infection of human beings, indicates that acquired immunity in tuberculosis per se can do little more than bring forces to bear which will inhibit the multiplication of virulent tubercle bacilli acquired by the individual and possibly increase the subsequent rate of their destruction. Although tubercle bacilli can eventually be destroyed by the body, the destruction of these microorganisms is not rapid, and viable tubercle bacilli may persist for prolonged periods in the tissues of individuals possessing a high degree of acquired immunity. Therefore, tuberculous disease may occur in the infected vaccinated individual at some subsequent period, if for some reason his resistance becomes lowered, in the same manner that it may occur in the individual who has acquired some immunity as the result of a controlled primary infection. The vaccinated individual, however, would have an advantage at the time of initial exposure to virulent mycobacteria because multiplication of the infecting tubercle bacilli would be inhibited immediately following their contact with the cells of the body. The period of rapid bacterial multiplication which will occur in the nonimmune individual before immunity develops would be avoided. Therefore, a vaccinated individual should harbor fewer virulent mycobacteria after exposure than a nonvaccinated individual who had received the same infecting dose. Vaccination will increase the number of individuals who will have the ability to inhibit the multiplication of virulent tubercle bacilli and should, therefore, produce a pro-

portionate reduction in the incidence of tuberculous disease in a population. The question of whether the immunizing power of BCG, or any other vaccine, is sufficient to bring about this desired result can only be answered by making observations on the incidence of the disease in vaccinated individuals as compared with the incidence in nonvaccinated people under conditions where the exposure to infection is equal.

Numerous controlled studies actually have been carried out to determine the efficacy of BCG vaccination for the prevention of tuberculosis in humans. Rosenthal[11] tabulates 29 such controlled studies in his recent book, and the reader is referred to this publication for full details. The majority of these studies show a lower incidence of tuberculous infection and tuberculous mortality in the vaccinated individuals as compared to the nonvaccinated individuals. Because of the impossibility of carrying out a completely objective evaluation of the efficacy of a vaccine such as BCG, all of these reports are subject to a greater or lesser degree of criticism. However, the cumulative weight of the evidence in favor of the effectiveness of BCG is impressive.

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Some of the more valid studies are: Ferguson's study on the vaccination of newborns in Canada,[102] Rosenthal and associates' studies on the vaccination of Negro and white newborns in Chicago,[103-105] Aronson and co-workers' studies on vaccination among American Indians,[106-108] Hyge's study on vaccination of school children,[109,110] the United States Public Health Service Studies in Puerto Rico,[111] Heimbeck's study of BCG vaccination in nurses,[112] and the recent British study.[100]

Space does not permit a critical analysis of the results of all of the studies on BCG vaccination. Instead, I have chosen the alternative of presenting some of the results of the latest and most properly conducted controlled study on the efficacy of BCG. This study was initiated in 1950 by the Tuberculosis Vaccine Clinical Trials Committee of the Medical Research Council of Great Britain and included nearly 56,000 male and female students at secondary schools between 14½ and 15 years of age (since the incidence of tuberculosis in Great Britain rises markedly at the age of 15). The experiment was carried out in the heavily populated areas of North London, Birmingham, and Manchester. Those children who had had known contact with a case of tuberculosis within 2 years were excluded from the trial. All eligible children were given tuberculin tests, and chest x-rays were taken. The first tuberculin test consisted of 0.1 c.c. of a 1:3,000 dilution of Old Tuberculin (3 TU). If negative to this strength, they were retested with 0.1 ml. of a 1:100 dilution of Old Tuberculin (100 TU). Those children found to be negative to the largest dose of tuberculin were divided into two groups according to the final digit of the serial number appearing on their record cards. The children of one group were vaccinated intradermally with 0.1 ml. (0.075 mg.) of a freshly prepared liquid vaccine which was obtained from the State Serum Institute in Copenhagen. Nearly 94 per cent of the participants were followed for the first 30 months, and a somewhat lesser number were followed over a period of 4 years. The children were examined three times, and a final tuberculin test and chest x-ray were taken. The films were reviewed by an independent assessor who was kept unaware of the results of the tuberculin test and did not know whether vaccination had been performed.

During the first 2½ years, there were 13 cases of tuberculosis amongst the BCG-vaccinated group, an annual incidence of 0.37 per 1,000; and there were 64 cases in the tuberculin-negative nonvaccinated group, an incidence of 1.94 cases per 1,000 children. During the period between 2½ and 4 years after the start of the study, 38 additional cases occurred in the unvaccinated group and 5 in the BCG-vaccinated group. This indicated that BCG vaccine retained its effectivness for as long as 4 years.

There can be no question that in this study the reduction in the incidence of tuberculosis was due to BCG. The random allocation of children to the two groups and the freedom from bias in the assessment of the occurrence of cases and the severity of cases makes any other conclusion impossible. One statement on the efficacy of BCG vaccination in this study reads as follows: "According to the present results, if none of the tuberculin-negative entries had been vaccinated, 165 cases of tuberculosis would have been expected among them within 30 months of entry. If all of them had received BCG vaccine, 30 cases would have been expected. The difference of 135 cases represents a reduction of 82 per cent in the incidence of tuberculosis in the tuberculin-negative group." Vole bacillus vaccine also was used on a smaller number of children, and its efficacy for the prevention of tuberculosis parallelled that of BCG although the local reactions obtained were somewhat more severe.

Results obtained from such a carefully conducted and controlled experiment can leave no doubt in the mind of an unbiased observer that BCG afforded a substantial protection against tuberculous infection. Taken together with the results of numerous other studies, the evidence to this effect becomes overwhelming. If we accept the conclusion that BCG vaccine may effect an 82 per cent reduction in the incidence of tuberculosis over a 4-year period, BCG then becomes one of the most effective vaccines available for the protection of man against an infectious disease.

Safety of BCG Vaccine.—Since BCG is composed of a living mycobacterium, the possibility that progressive disease might occur following administration has always been of concern to workers in the field. As pointed out by Rosenthal,[11] the size of the vaccine lesion will vary with the age and race of the recipient, the source of the vaccine, the dose of the vaccine, and the technique of administration. Following administration of the vaccine at a single intradermal site, ulceration may occur in from 40 to 75 per cent of the recipients.[106,113] Regional lymphadenitis, sometimes with abscess formation and suppuration, may occasionally occur. Some cases of lupus vulgaris occurring at the site of BCG inoculations have also been reported.[113] Use of the multiple puncture method of inoculation appears to have almost completely eliminated the foregoing complications.[11]

There is little evidence to indicate that progressive tuberculous disease frequently follows inoculations with BCG. The epidemic which occurred in newborns in Lübeck, Germany, in 1930, following the administration of BCG has definitely been shown to have resulted from the substitution of a virulent strain of *Mycobacterium tuberculosis* for the BCG strain.[114]

More recently from the Scandinavian countries, 4 cases have been reported of progressive tuberculous infection which resulted fatally in individuals pre-

viously vaccinated with BCG. From these cases organisms resembling BCG were isolated. These cases have been reviewed by Ustvedt[113] and Rosenthal.[11] There is no way in which we can be certain that these deaths were the result of infection produced by BCG since there is no specific characteristic which can be used for the identification of the BCG organism. Rosenthal[11] has pointed out that these cases might have resulted from infection with atypical acid-fast bacilli since the occurrence of such infections are being recognized with increasing frequency. However, even if these cases were actually the result of infection with BCG, the record of 4 deaths out of more than 100 million people vaccinated would earn for BCG a greater safety record than that recognized for smallpox vaccine.

Allergenicity of BCG Vaccine.—Objections have been made to vaccination with BCG because it will induce in those vaccinated a substantial degree of allergy to tuberculin. This on the one hand would eliminate the use of the tuberculin test as a diagnostic tool in vaccinated individuals, and, on the other, would reduce the usefulness of the tuberculin test for the determination of the degree of tuberculous infection in a population group or community. The first objection would seem to be a minor one since there are other and better procedures whereby tuberculous disease can be differentiated from other clinical conditions. In this connection it is well to recall that the tuberculin test is mainly significant in the negative sense. That is, a negative tuberculin test may help to rule out tuberculous infection, but a positive test does not establish the presence of tuberculous disease.

The second objection is somewhat more valid, particularly in areas where the rate of tuberculous infection is low. Under these conditions the detection of the small proportion of infected individuals by means of the tuberculin test becomes worth while. Other tuberculosis control methods then can be limited to this small group of tuberculin-positive individuals and their contacts. Where the incidence of tuberculous infection is high, however, as in many of our large cities, the determination by means of the tuberculin test that the majority of the population is infected is of little value since the appropriate control measures can be applied just as easily to the whole population as to the majority found to be tuberculin positive. The tuberculin test is not a particularly useful instrument under such conditions, and the use of BCG vaccine in such a population creates little or no problem.

Finally, the question should be seriously considered whether an 80 per cent reduction in the incidence of tuberculous disease, as suggested by the British study,[100] might not more than compensate for the lack of the usefulness of the tuberculin test for the determination of the incidence of infection.

Usefulness of BCG Vaccine.—Although widely employed in many European and Asian countries as a protective agent against tuberculous infection, the acceptance of BCG for this purpose has not been universal. In the United States, in particular, recommendations for its use have generally been restricted to those individuals who are more frequently exposed to infection, such as doctors, nurses, medical students, and technicians. In the civilian population, recommendations for its use have been limited to those areas where the incidence of tuberculosis is particularly high as, for example, in some of the big cities.[115] Furthermore, only

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in recent years has it been used to any appreciable extent among individuals whose occupation entails a high risk of exposure to tuberculosis. In addition to doubts about efficacy, safety, and allergenicity of BCG vaccine, the usefulness of this agent has been questioned on the basis that since the majority of cases of tuberculosis now occur among tuberculin-positive individuals, BCG vaccination of the tuberculin-negative portion of the population would not exert much influence on the incidence of the disease.[111,116-118]

However, to abandon the principle of vaccination for this reason is to miss the point that had the tuberculin-positive individuals been vaccinated prior to the time of their initial exposure to virulent tubercle bacilli, the incidence of tuberculous disease in this group might have been reduced to an appreciable degree. This situation actually provides a strong argument for the vaccination of infants and children against tuberculosis with revaccination at suitable intervals in order to maintain as high a level of immunity as possible. Such a procedure, if instituted now, might not produce an immediate large effect on the incidence of tuberculosis, but if the results of the British study are true criteria of the effectiveness of BCG vaccine, it might easily result in a future decrease in the incidence of tuberculosis of significant proportions.

Even though such a program might have an appreciable influence on the incidence of the disease in the United States in the next generation, it should never be considered a substitute for the time-honored and time-tested principles of tuberculosis control. The detection, isolation, and treatment of active cases to render them noninfectious, must always be recognized as the most effective tuberculosis control methods. But as an adjunct to such procedures, particularly in areas where they are difficult to apply effectively, vaccination with BCG has received too little attention.

There is a real need for a vaccine against tuberculosis which would contain no viable organisms and which would not be allergenic. Such a vaccine could be administered more easily and without regard to the state of tuberculin hypersensitivity of the individual, and its use would not limit the value of the tuberculin test. Intensive efforts are being made to develop such a vaccine in several laboratories. However, in the meantime, it would seem reasonable to make more extensive use of BCG vaccine, since it is effective and safe. There is little reason why it should not become as standard a part of good pediatric practice to administer BCG vaccine in areas where the incidence of tuberculosis is high, as it is to vaccinate infants and children against smallpox, diphtheria, tetanus, and whooping cough.

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Editorial

THE WESTERN RESERVE APPROACH TO TEACHING MEDICAL STUDENTS ABOUT LONG-TERM ILLNESS

Medical students are stimulated and challenged by the fascinating intricacies of pathology and by the exciting task of evaluating and instituting appropriate treatment for the "fresh case," that newly arrived patient whose glamour has not been dulled by some colleague's diagnostic label.

Much of what is done in medical schools tends to emphasize this diagnostic game. The relatively brief stay of patients in general hospital wards, the rapid rotation of student assignments, and the obvious difficulties of adequate follow-up of individual ward patients tend to focus attention on elaborate work-up of the "new" patient and prompt discharge to make room for another "interesting problem." The many elderly patients with persistent disability in the general ward population tend to be relegated to the "crock" category, unless they manage to have some unexplained fever or bizarre electrolyte disturbance.

The students accept this pattern with enthusiasm, in part because of their natural desire for new experience with disease, and in part because of the example set by interns, residents, and visiting staff of teaching hospitals. These men are products of the traditional educational system where the principal clinical teaching exercises are focused on diagnosis and acute treatment. Even when the senior physicians are heavily involved in long-term management of patients with chronic disease in hospital specialty clinics or private practice, the students seldom have significant contact with such activities, unless, as individuals, they are fortunate enough to come under the influence of a dynamic teacher who is conducting laboratory or clinical research on some aspect of these diseases.

It is not easy to modify this medical school pattern, since time is short and every student should have broad opportunity to apply his knowledge and skill in the traditional clerkship methods. Even more important is the fact that when efforts are made to teach management of long-term illness, it is difficult to provide for students the kinds of excitement and satisfaction which will balance the always-present complexities, frustrations, and failures.

In attempting to deal with this pedagogic problem, the Western Reserve faculty emphasized three points: continuity of relationship between the student, the patient, and a clinical preceptor; a significant and responsible role for the student in the management of the patient's problem; and ample support for the student in efforts to develop constructive plans for rehabilitation of his long-term patients.

To work toward these objectives, specific methods were introduced into the curriculum. Beginning on February 1 of the junior year, the class is divided into groups of eight, each of which has a clinical preceptor. Each group has a specific

afternoon (e.g., Monday) for the "Continuity Program" each week, right through to the end of the senior year. On that afternoon the group has available to it the "Continuity Clinic" which is a special section of the outpatient department staffed and equipped so that the student may conduct an office practice there under the guidance of his preceptor. The student is in effect the general physician for his patients, with all the resources of the teaching hospital available to him.

Each student is expected to have a limited number of patients, including one or two with chronic disability. To assist the student and preceptor in evaluating these patients and planning comprehensive care including rehabilitation, there is a teaching team consisting of physician, medical social worker, public health nurse, physical therapist, and vocational counsellor. Members of this group, supported by a Rehabilitation Teaching Grant from the National Foundation for Infantile Paralysis, have no specific service obligations but act as consultants and advisors to the student, especially about community resources for rehabilitation.

Two classes have now completed this part of the curriculum and a third began it on Feb. 1, 1957. The operation of this program is administratively difficult, but the students assume a large part of the responsibility for management of the individual patients, and with the experience of the past two years the staff has been able to develop smoothly working machinery. The preceptors are all internists, many of them members of the "part-time" staff and well-prepared to guide the student in medical care of his patients.

As usual in educational efforts, the most obvious benefits accrue first to the teachers. The preceptors in the Continuity Program have been almost unanimously enthusiastic about the potentialities of this type of teaching, have felt that they learned a great deal about comprehensive care themselves, and have enjoyed their opportunity to work closely with the same small group of students for a 16-month period.

The student reaction to the program has been variable. The obligations to the Continuity Clinic obviously complicate the students' lives, making it necessary for them to arrange to be away from clerkship activities one afternoon each week. Some students find it impossible to see any benefits from the Continuity Program which balance the losses which come from interruption of their "regular" work. As would be expected, some students, like some of their older colleagues, are depressed when patients fail to respond promptly to their ministrations. They become unhappy about their inability to see dramatic results of therapy. On the other hand, many students have had most significant and gratifying experiences with patients who have derived a type of benefit from the Continuity Program which they clearly would not have found under most circumstances in teaching hospital clinics.

The following is extracted from a report submitted by members of the Class of 1957 Student Committee on Medical Education: "The most favorable comments about the Continuity Clinic seemed to come from students who had a large number of patients (6 or 7) and a large variety of interesting long-term medical problems. Most students seemed to place the greatest learning value upon the actual medical treatment of chronically ill patients and considered problems of

rehabilitation to be of much less interest." This would suggest that some progress has been made in drawing student attention toward management of chronic disability but that not all students can see clearly the obligations of the physician in comprehensive care.

In an entirely separate area of the Western Reserve curriculum, some students have found another means to become interested in the problems of chronic disease. This is the required "project" which was introduced to give each student an opportunity to have some experience in scientific investigation under the guidance of a member of the faculty. One day per week for a total of 32 weeks in the first and second years is set aside for these projects. During these same years they also have one and one-half days of "free time" each week. Many of the students choose to use some or all of this free time for their projects. During the five years this program has been in operation, many of the projects have been concerned with basic studies related to heart disease, arthritis, muscular dystrophy, diabetes, and other long-term diseases. There is no doubt that this research approach to the mechanisms underlying these chronic disorders and to the precise evaluation of their clinical, psychologic, social, and vocational ramifications is one kind of antidote to the superficiality of interest in them encountered in some general hospital ward services.

Maturity involves the ability to forego immediate rewards in order to achieve highly valued long-range goals. Since medical school presents the student with many challenging and demanding situations where immediate goals are obvious there will always be difficulty in getting new recruits to turn much of their attention to medical areas in which satisfying results, if any, lie far in the future. This has been obvious in connection with teaching about preventive medicine and psychiatry, where significant learning also demands some maturity on the part of the student. If medical educators do decide that it is desirable to teach medical students about chronic disease, they will face the problem of helping the student develop early the kind of maturity about professional obligations which we expect in our best practitioners, teachers, and investigators. The Western Reserve Continuity Program is attempting to do this by putting the student in a continuing and responsible relationship with selected patients in a setting which gives him the role of a general physician under the guidance of an experienced preceptor. On a more restricted basis, the required "project" has enabled some students to become interested in chronic diseases by gaining an appreciation of the complexity and scope of the problems they present. It is gratifying that many students have responded in a remarkably mature and effective way to these learning opportunities.

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Book Reviews

PROCEEDINGS OF THE THIRD NATIONAL CANCER CONFERENCE. Philadelphia, Pa., June, 1956. J. B. Lippincott Co. Pp. 961. Price $9.00.

As its title implies, this volume contains a record of the various lectures and symposia concluded during the National Cancer Conference held in Detroit in June, 1956. The conference topics were varied and included considerations of most of the commonly occurring human malignancies as well as discussions of the fundamental biologic phenomena of neoplasia. Contributions were forthcoming from an equally varied group of participants and thus were set forth the views of the laboratory scientist, the clinical investigator, the practicing physician, surgeon, and radiologist, as well as the public health officer and the biometrician. Of particular interest, perhaps, were the presentations relevant to the efficacy of cytologic screening techniques, the increasing body of knowledge derived from epidemiologic investigations, and the implications inherent in Dr. Stanley's belief that "the time has come when we should assume that viruses are responsible for most, if not all, kinds of cancer." The currently held tenents regarding the control of cancer by means of surgical, radiologic, and chemotherapeutic techniques were restated, but equally emphasized was the need for proper clinical evaluation of the various therapeutic measures employed.

In general, the subject matter is clearly presented, amply illustrated, and accompanied by a selected bibliography. Much of the material distilled into this conference appears in print elsewhere. However, these Proceedings are of additional value in that they have preserved the discussions of the various panel members and have provided the reader with easy access to the current body of information relevant to cancer and cancer research. Of even greater value, one would hope, are the benefits to be derived from the "nonrecorded proceedings" engendered by the meeting of men of many disciplines to consider a common problem.

Albert H. Owens, Jr.

CLINICAL CARDIOPULMONARY PHYSIOLOGY—Sponsored by the American College of Chest Physicians. Edited by Burgess L. Gordon, M.D. 768 pages, 248 illustrations, 32 tables. New York and London, 1957, Grune & Stratton, Inc. Price $15.75.

This book has some merits and some demerits as a consequence of its nine editors and fifty-two contributors; the coverage is wide but spotty. So many of the general medical aspects of cardiac and pulmonary diseases are discussed that one is led to infer that medicine and clinical physiology are fast becoming synonymous in the cardiopulmonary field. This reviewer has no fault to find with this trend, provided the medical physiologists do not lose sight of the enormous importance of the doctor-patient relationship in diseases with such frightening symptoms as dyspnea, palpitation, and pain in the chest. However, if one is to make clinical physiologists out of medical men, then certainly the physiologic interpretation of clinical signs and symptoms should feature prominently. This synthesis is scarcely attempted with respect to pulmonary dysfunction. Dayman makes the striking comment "that it will be some time before applied physiology discovers the physical examination" and then, by failing to enlarge on this theme, he assures the continued validity of his assertion. Only in the opening paragraphs of a superb chapter on Acquired Valvular Heart Disease is note taken of the extent to which clinical physiologists are, and should be, working themselves out of a job by improving clinical acumen. Having remarked on this omission, one can only marvel at the amount of material which does appear between the covers of this fat book. Of the recent publications in its field, this is the most all-inclusive. It will be useful for reference purposes, but the reader frequently will find it necessary to make use of his own critical faculties.

Richard L. Riley

BRITISH MEDICAL BULLETIN—PHYSIOLOGY AND PATHOLOGY OF THE KIDNEY. Vol. XIII, No. 1. London, 1957. Published by the Medical Department, The British Council. Pp. 74. Illustrated. Price $3.25.

This symposium, comprised of 16 papers, was written by clinicians or others "in close touch with clinical departments." A few of the papers deal only with clinical studies, some discuss only studies in experimental animals, while others are based on both approaches. As a group they are another indication that advances in technology and clinical thinking not only are making clinical problems subject to scientific investigation, but also are leading clinicians into an attitude which permits them to oscillate freely between the clinic and the basic research laboratory. In the Introduction, Professor Robert Platt, who was Chairman of the committee that planned this symposium, states that the kidney leads its serious students into the study of many different scientific disciplines, both basic and clinical, and suggests that this approach may well be one of the answers to the problem of avoiding narrow isolation in this time of increasing specialization. The symposium gives ample support to this thesis. Perhaps not too surprisingly, similar thoughts are presented in the Introductions to two other recent symposia on the kidney (Symposium on The Nutritional Aspects of Kidney Disease, J. Clin. Nutrition, **4**:463-596, 1956, and Symposium on Glomerulonephritis, J. CHRON. DIS. **5**:1-172, 1957.

All but one of the papers of this symposium are rather brief, varying in length between 2 and 6 pages. The exception is a 10-page article on the nephrotic syndrome by Squire, Blainey, and Hardwicke who present, among other considerations, an analysis of 44 patients they studied during a 4-year period.

Because of the brevity of the articles, only a few contain unpublished data. However, they all represent concise and thoughtful presentations of the current thinking and knowledge deemed important by experts in the 16 different fields covered in the symposium. In many instances selected major points are documented by data presented in tables and diagrams. Seven of the articles are illustrated by excellent and useful photographic plates.

McCance and Widdowson present, appropriately in the first article, not only data but interesting and new concepts concerning renal function and homeostasis during the early days of life. Their thoughts undoubtedly will be of practical benefit to pediatricians. Also appropriately, in the last article, Kennedy presents intriguing data and thought on the similarity of the effects of old age and of overnutrition on the kidney. The reviewer believes that pursuit of Kennedy's approach should lead to considerable advance in the problem of senescence in at least one organ.

Four of the papers deal with problems of fluid and electrolytes, all of which present data and viewpoints are not readily available in texts or monographs. Two papers discuss the current status of experimental hypertension while one discusses the treatment of hypertension in primary renal disease. Interesting anatomic findings in several diseases as revealed by microdissection of the nephron is the subject of one paper, while others represent considerations of renal aminoaciduria, the nephrotic syndrome, and the pathogenesis of urinary calculus formation. Currently there is considerable basic research activity in the latter field. In an article on azotaemic renal osteodystrophy, Stanbury presents his personal concepts and considerable evidence which suggest that interpretation of such lesions is not as simple nor as well documented as some American investigators have been led to believe. Finally, the roles of renal angiography and of venography in the diagnosis of renal diseases are carefully considered in two papers.

This symposium should be valuable to everyone interested in renal diseases, not only because of the critical review of pertinent knowledge and of the current thinking of experts, but also for a number of points that can be put to practical use in the clinic.

D. P. Earle, M.D.

Announcement

AVAILABILITY OF SYMPOSIUM NUMBERS

Since the first publication of this JOURNAL in January, 1955, several entire issues have been devoted to Symposium numbers on topics of major interest. These Symposia are usually complete discussions, which cover conflicting points of view if necessary, which often include some original work of the several authors as well as up-to-date presentation of the literature (more current than is obtainable even in recently published textbooks), and which in general may be expected to remain scientifically valid for two or more years. The Symposia are of especial value to teachers and to medical students, as well as to practitioners.

Those so far published, with dates of publication, Guest Editors, and Symposium title, are listed here.

May, 1955 (Guest Editor, David Seegal): The Management of Patients with Pr' ıary (Essential) Hypertension. (Out of stock.)

October, 1955 (Guest Editors, Lester Breslow and Dean W. Roberts): Screening for Asymptomatic Disease. (Of special interest to public health officers and to hospital clinics.) (14 issues in stock.)

July, 1956 (Guest Editor, Louis Lasagna): Pain and Its Relief. (106 issues in stock.)

October, 1956 (Guest Editor, Robert L. Levy): Coronary Heart Disease. (26 issues in stock.)

January, 1957 (Guest Editors, David P. Earle and David Seegal): Glomerulonephritis. (Out of stock.)

April-May, 1957 (Guest Editor, David T. Smith): Chronic Fungus Infections. (180 issues in stock.)

June, 1957 (Guest Editor, Joseph J. Bunim): Rheumatoid Arthritis. (480 issues in stock.)

October, 1957 (Guest Editors, Maxwell M. Wintrobe and Carl V. Moore): The Management of Hematologic Disorders. (300 issues in stock.)

These several Symposium numbers, together with others to appear in future issues, may be separately purchased at $2.00 per single copy (while the supply lasts). Orders should be sent directly to the publisher, The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis 3, Missouri.

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